LIBRARY
SEP 20 1951
NATIONAL INSTITUTES OF HEAL.

ACTA RADIOLOGICA

Redactores

Å. ÅKERLUND, Stockholm — E. BERVEN, Stockholm — T. DALE, Oslo — J. FRIMANN-DAHL, Oslo

R. GILBERT, Genève — L. G. HEILBRON, Amsterdam — J. W. F. HEUKENSFELDT JANSEN, Amsterdam

G. JANSSON, Helsingfors — C. KREBS, Aarhus — S. MUSTAKALLIO, Helsingfors

P. FLEMMING MÖLLER, København — GISLI FR. PETERSEN, Reykjavik — H. R. SCHINZ, Zürich

Editor

GÖSTA FORSSELL †

Acting Editor: E. BERVEN, Stockholm

Collaborant

IN DANIA: JENS NIELSEN, Köbenhavn; FLEMMING NÖRGAARD, Köbenhavn; K. OVERGAARD, Viborg.

IN FENNIA: Y. LASSILA, Helsingfors; K. SETÄLÄ, Helsingfors; CARL WEGELIUS, Helsingfors.

IN HELVETIA: L. BABAIANTZ, Lausanne; M. LÜDIN, Basel; A. ZUPPINGER, Bern.

IN HOLLANDIA: G. F. GAARENSTROOM, Amsterdam; S. KEIJSER, Groningen; H. W. STENVERS, Utrecht.

IN NORVEGIA: S. BAKKE, Bergen; ERIK POPPE, Oslo; H. REITAN, Oslo.

IN SUECIA: FOLKE KNUTSSON, Upsala; ERIK LINDGREN, Stockholm; OLLE OLSSON, Lund.

Vol. XXXV — May—June 1951 — Fasc. 5—6

Stockholm: P. A. Norstedt & Söner

ACTA RADIOLOGICA

Subscriptions and communications should be addressed to Acta Radiologica, Stockholm 2, Sweden.

Vol. XXXV. May—June 1951 Fasc. 5—6

INDEX

Pagina

Atypical Hurler's syndrome. A report of 3 cases with a discussion of the differential diagnosis by Gregers Thomsen and Jørgen Vesterdal 331

Equipment for microradiography with soft roentgen rays by A. Engström and L. Wegstedt 345

Observations on the skin reaction to the subcutaneous application of metallic polonium in mice by Leiv Kreyberg and Finn Devik 356

Pyelo-ureteritis cystica by G. Fr. Petersen 363

Hodgkin's disease of the oesophagus by Jørgen Bichel 371

The mesothorium-radium beam unit by F. Běhounek and J. Klumpar 375

Radiographic findings in 14 cases of Sturge-Weber syndrome by Giovanni Di Chiro and Erik Lindgren 387

Vertebral hemangioma with compression of the spinal cord. Report of a case treated with roentgen with good clinical results by Inge Lindqvist 400

Neurosarcoma duodeni by Allan Elliot and Carl Johan Hansson 407

The effect of various factors on the roentgenological determination of the cardiac volume by Sven Roland Kjellberg, Henrik Lönroth and Ulf Rudhe . . . 413

Roentgen rotation therapy in cancer of the esophagus. Dosage problems. Preliminary results by Inge Gynning 428

Roentgen rotation therapy in cancer of the hypopharynx by Inge Gynning . . 443

A new method for the treatment of cancer of the lungs by means of artificial radioactivity (Zn^{63} and Au^{198}) First experimental and clinical studies by J. H. Muller and P. H. Rossier 449

Rudolph Grashey. In Memoriam by Rolf Glauner 469

7th International Congress of Radiology, 1953. Preliminary notice 472

ACTA RADIOLOGICA, published by *the Societies for Medical Radiology* in *Denmark, Finland, Holland, Norway, Sweden* and *Switzerland,* contain articles pertaining to *roentgenology, radium therapy, light therapy,* and *electrotherapy.* These articles are published in English, French or German according to the decision of the author. From 1948 on, *two* volumes appear annually. Each volume comprises about 500 pages, distributed in six numbers. *Subscriptions* may be forwarded to Acta Radiologica, Stockholm 2, Sweden. **Subscription rate per Vol.:** *35 Sw. crowns, postage 3 Sw. crowns additional for non-Scandinavian countries, payable in advance. Single copies 7 Sw. crowns plus postage. The subscription will be considered renewed if it has not been cancelled at the latest 10 days before the beginning of a new volume.*

ACTA RADIOLOGICA, herausgegeben von den *Gesellschaften für medizinische Radiologie* in *Dänemark, Finnland, Holland, Norwegen, Schweden* und in der *Schweiz,* enthalten Arbeiten auf den Gebieten der *Röntgenologie, Radiumtherapie, Lichttherapie* und *Elektrotherapie.* Die Beiträge werden je nach eigener Wahl des Verfassers, in deutscher, englischer oder französischer Sprache veröffentlicht. Ab 1948 erscheinen *zwei* Bände jährlich. Jeder Band enthält za 500 Seiten, in sechs Heften erscheinend. *Abonnement* bei Acta Radiologica, Stockholm 2, Schweden. **Abonnementspreis je Band:** *35 schw. Kronen, zuzügl. Postgebühren, 3 schw. Kronen für nicht-Skandinavische Länder, im voraus zu bezahlen. Einzelne Hefte 7 schw. Kronen zuzügl. Postgebühren. Die Zeitschrift wird den Beziehern bis zur Abbestellung geliefert; diese muss spätestens 10 Tage vor Beginn eines neuen Bandes bei der Redaktion eingehen.*

ACTA RADIOLOGICA
EDITA PER SOCIETATES RADIOLOGICAS DANIÆ, FENNIÆ, HELVETIÆ, HOLLANDIÆ, NORVEGIÆ ET SUECIÆ

VOL. XXXV MAY—JUNE 1951 FASC. 5—6

ATYPICAL HURLER'S SYNDROME[1]

A report of 3 cases with a discussion of the differential diagnosis

by

Gregers Thomsen and *Jørgen Vesterdal*

Hurler's syndrome which was first described by HURLER (1919) and PFAUNDLER (1920) is a systemic disease of congenital origin with the following characteristics: moderate dwarfism with abnormal proportions, enlargement of the liver and spleen, corneal opacity, impaired hearing and mental retardation. The head is large with a prominent forehead and a plump face. The eruption of the teeth is delayed, the teeth being small with broad interdental spaces. The abdomen is prominent. A kyphosis is present in the upper lumbar region. The movements of the joints are limited, particularly in the fingers causing a claw-like appearance of the broad hands. The general appearance of the patient is rather grotesque and accounts for the designation »gargoylism» (gargoyle: a grotesque figure).

Roentgen examination shows a series of abnormalities in the whole skeleton: the skull is large, often thick-walled, with protruding forehead and supraorbital ridges. A prominent ridge may be present in the midline at the sagittal suture. The form of the skull is often scaphocephalic or oxycephalic. The sella is large and deep. There is hypertelorism. In the upper part of the lumbar column a characteristic kyphosis is seen. The vertebrae in this region are frequently deformed partially due to the absence of some of the limbus centres of ossification of the vertebral bodies. The ribs are broad and club-shaped, like palm leaves or the blades of a scythe. The bones of the extremities are short and thick with a coarse dense structure. The corticalis is enlarged so that the diaphysis is as broad as the metaphyses. These abnormalities are most pronounced in the upper extremities, particularly in the metacarpal bones which

[1] Submitted for publication, Oct. 27, 1950.

From the Radiological department (Director: Prof. FL. MØLLER) and the Pediatric department (Director: Prof. P. PLUM), the University hospital (Rigshospitalet), Copenhagen, Denmark.

are quadrate or even bottle-shaped. The proximal epiphyses of the humerus and the femur are often deformed. Coxa valga may be present.

By pathological examination some authors (KRESSLER & AEGERTER and others) have found an unknown substance, presumably a lipoid, in the cells of the brain and in the parenchyma cells of almost all the other organs, and the disease thus seems to be closely related to the lipoidoses. This accounts for the term »lipochondrodystrophy». In cases without corneal opacity it may, however, be impossible to demonstrate the lipoids (DE LANGE & al.) Abnormal granulation of the lymphocytes have been reported by GASSER & ZELLWEGER and other authors.

Thus the typical cases represent a series of signs which are so characteristic that the diagnosis is easily established.

But in addition to these, forms exist where some of the symptoms are absent, and in these cases difficulties with regard to the differential diagnosis will arise. Hypothyroidism and chondrodystrophy will, from our experience, present the chief difficulties and this is in accordance with the experience of other authors (NOTTER, CAFFEY).

On account of these diagnostic problems we have considered it to be of some value to publish three more or less atypical cases of Hurler's syndrome observed in the Pediatric and Radiological Departments of the University Hospital, Copenhagen. In addition, we have looked over our cases of hypothyroidism and chondrodystrophy in order to see the similarities and evaluate the signs in the differential diagnosis.

Case Reports

Case no. 1. ♂ E. E. J., born 28/7 1942 (J. no. 50/49). No similar cases in the family. Healthy parents. The eldest of three children: the two others (a boy and a girl) healthy. Birth weight 3,500 gms. Normal delivery. He could sit erect and walk at the normal time, but later he was found to be mentally backward; he was therefore admitted to a county hospital, where he was considered to be a case of endocrinopathy, possibly Cushing's disease.

On examination on admission to the University Hospital, Jan. 1949 (Fig. 1 a): Height 108 cm (normal 109 cm) and weight 20.5 kgms (normal 18.5 kgms). He is mentally backward (Bühler-Hetzer: 53). The head is large and brachycephalic. The hair is bristly and the hairline reaches far down on the forehead. The bridge of the nose is broad and flat, the lips are thick, and the tongue moderately enlarged. The soft palate is cleft. The neck is short. Chest: nothing particular noted. Prominent abdomen with enlargement of the liver and spleen. The extremities are plump, the hands broad and thick, and the fingers crooked, their extension being impaired. The motion of the hip joints is limited, particularly rotation. Slight lumbar kyphosis only noted.

Laboratory findings: Hgb. 90 %. Sedimentation rate 9 mm/1 hr. Blood cholesterol 247—157—240 mg per cent. Blood pressure: syst. 95, diast. 55 mm. Urine: no abnormality. Tuberculin reaction negative.

Ophthalmological examination: no corneal opacity or other abnormalities. Otological examination: normal; no impairment of the hearing.

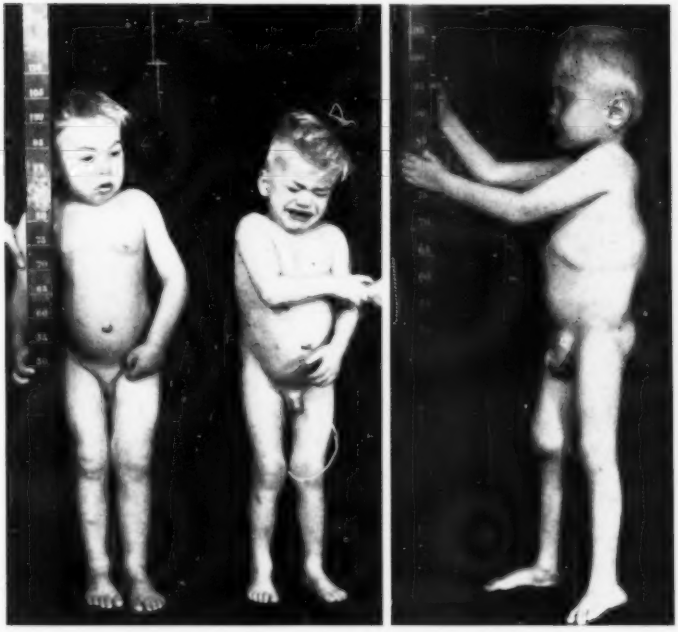


Fig. 1 a & b. Fig. 1 c.

Fig. 1. a) Case 1 ($6^1/_2$ years old). b) Case 2 ($3^3/_4$ years old). c) Case 3 ($4^1/_2$ years old).

Radiological examination. The skull is large and thick-walled, and of a brachycephalic shape. The sutures are normal, the sella turcica is large and flat, but without signs of erosion. Moderate hypertelorism present. Normal eruption of the teeth, but the persisting deciduous teeth are small with enlarged interdental spaces.

Slight kyphosis present; the first lumbar vertebra deformed, and the lower limbus ossification centre absent (Fig. 2). The remainder of the vertebrae appear normal. The ribs are broad and club-shaped. Examination of the stomach, the small intestine and the colon shows no abnormality. In the abdominal film an enlargement of the liver and spleen is noted (Fig. 3).

Upper extremity: The humerus, radius and ulna are broad and thickened, the breadth of the diaphyses being increased. The epiphyseal centres are irregular, but their ossification is not delayed. The metacarpal bones and the phalanges are broad, short and quadrangular. The fingers are crooked. The ossification of the carpal bones is slightly delayed.

Lower extremity: The sutures of the pelvis are very broad. The inferior rami of the pubis and the ischium are separated by about a centimetre. The acetabulum and the epiphysis of the femoral head are slightly irregular (Fig. 4). Coxa valga are present. The trochanteric apophysis is not ossified. The femur, the tibia and the fibula are thickened. In the feet abnormalities resembling those of the hands are present.

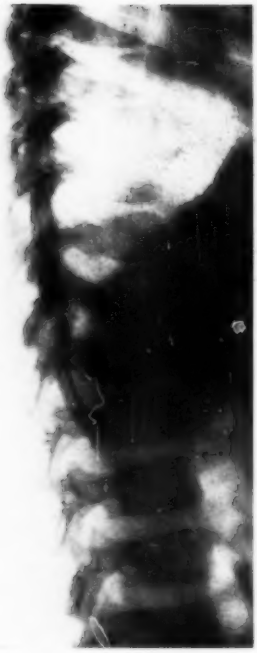


Fig. 2.

Fig. 3.

Fig. 2. Case 1. Kyphosis of the first lumbar vertebra.
Fig. 3. Case 1. Broad ribs, enlarged liver and spleen.

The spongy bone structure is rather coarse and the compacta thicker than normal, particularly in the long bones.

Case no. 2. ♂ F. K. L., born 5/5 1945 (J. no. 38/49). No similar cases in the family. The fourth of four children (a brother died 4 months old, presumably from heart failure; two sisters normal). Birth weight 3,750 gms. Uncomplicated delivery. He could sit and stand at the normal time. The parents believe him not mentally backward; his hearing is severely impaired; this was first noticed at the age of $1\frac{1}{2}$ years.

Examination on admission to the University Hospital, Jan. 1949 (Fig. 1 b): Height 100 cm (norm.: 98 cm). Weight: 19.5 kgms (norm.: 16 kgms). Mentally he is normal or only slightly backward. Bühler-Hetzer test is 85 %, but the examination is impeded by his hearing; he is almost completely deaf and reacts only slightly to loud noises. He cannot speak intelligibly. His appearance is most grotesque, particularly when he cries. The head is large and brachycephalic, with the bridge of the nose depressed. The mouth is broad and the lips thickened. The hair is bristly and the eyebrows heavy. The teeth are small with large interdental spaces; cleft soft palate noted. Chest: no changes. The abdomen is prominent with swelling of the liver and spleen. There is a very slight lumbar kyphosis. The extremities are a little slender, the hands are broad and plump, and

Fig. 4. Case 1. Coxa valga; slight irregularity of the epiphyses of the femoral head and acetabulum; coarse bone structure.

the fingers crooked and with limited extension. The fifth fingers are radially incurved; the movements of the hip joints limited.

Laboratory findings: Hgb. 88 %. Sedimentation rate 10 mm/1 hr. The Wassermann and the Moro reaction are negative. Blood pressure: syst. 110, diast. 55 mm. Blood cholesterol 157 mg per cent. Urine: no abnormality.

Ophthalmological examination: no corneal opacity or other change. Otological examination: the ears appear normal.

Radiological examination. The skull is large, but of normal shape. The sella is large, and the supraorbital ridges prominent. Hypertelorism is present. The teeth are small with enlarged interdental spaces.

In the spinal column a slight kyphosis is noted around the first lumbar vertebra (Fig. 5). The shape of the vertebral bodies and the limbus centres are both normal. The ribs are broad and club-shaped to a moderate degree only. Examination of the stomach, small intestine and colon reveals no changes. An enlargement of the liver and spleen is seen in the roentgenograms of the abdomen.

Upper extremity: The humerus, radius and ulna are enlarged and shortened (Fig. 6). The metacarpal bones and the phalanges are stunted and quadrangular. The fingers are crooked (Fig. 7): ossification of the carpal bones slightly delayed.

Lower extremity: the sutures of the pelvis are broad. The inferior rami of the pubis and the ischium are separated by about a centimetre. The epiphysis of the femoral head is irregular and coxa vara of a moderate degree is present. The trochanteric apophysis is just visible. The femur, tibia and fibula are broad and thickened.

The bone structure is coarse, and the calcium content increased.

Fig. 5. Case 2. Slight kyphosis, but no deformity of the first lumbar vertebra (arrow).

Case no. 3. ♂ J. A. H., born 27/8 1943 (J. no. 435/48). Two male cousins of the mother's mother are said to have been small crooked cripples with large heads. The patient is the only child of healthy parents. Birth weight 3,700 gms. Uncomplicated delivery. When he was 3 months old, his parents noticed that his head enlarged. At the age of 6 months he developed a spinal curvature in his attempts to sit upright. He was believed to have rickets and was given vitamin D and light treatment.

In the period from May 1944 to May 1948 he was admitted six times to the Pediatric Department of the University Hospital.

Examination on the first admission (9 months old): Height 77 cm (norm.: 70 cm), weight 11.8 kgms (normal for the height: 10 kgms). He is mentally backward, but not quite an imbecile. His muscles are weak, and he cannot sit upright, but is just able to hold his head erect. The skull is large and brachycephalic, without craniotabes, and by radiological examination the wall is found to be of normal thickness but very dense. The anterior fontanel measures 4 by 4 cm. The bridge of the nose is broad and depressed. The abdomen is large with enlargement of the liver, but there is no splenomegaly. An inguinal hernia is present on the left side. The spinal column flexes considerably when the patient attempts to sit. The extremities appear to be normal. No abnormality is found ophthalmologically. The Wassermann and the Moro reactions are negative. Urine: normal. Hgb. 78 %.

Development after the first admission: He was first able to sit upright at the age of 23 months. The enlargement of the liver persisted up to the age of 3 years, but after that no hepatomegaly was found. Enlargement of the spleen also persisted from 23 months to 4½ years.

At the age of 23 months ophthalmoscopy revealed a slight optic atrophy on both sides, perhaps a sequel of a papilloedema due to premature synostosis of the skull which was now oxy-brachycephalic.

At the age of three, he could say a few words. At this age, he developed a chronic hydarthron of the right knee without osseous abnormalities in the joint.

Examination on the sixth admission (4½ years old) (Fig. 1 c): Height 103 cm (norm.: 110 cm), weight 20 kgms (normal for the height: 17 kgms). He is mentally backward to a considerable degree (Bühler-Hetzer: 33). Sight and hearing seem to be normal. The gait is bad and waddling, partly due to a chronic hydarthron of the right knee. The head is large and broad (head circumference 57.5 cm), with a prominent ridge in the mid-line at the sagittal suture. The bridge of the nose is flat and depressed. The upper lip is shortened, making the mouth triangular in shape. The teeth are small with defective enamel and caries. The neck is short. A sinistro-convex kypho-scoliosis is present

Fig. 6. Case 2. Thickened, broad bones of the upper extremity.

in the dorso-lumbar region. Chest: no changes seen. The abdomen is prominent, but without enlargement of the liver and spleen. The upper extremities are slight. The hands are not deformed and the fingers are slender without limitation of movement. The lower extremities are also slight, but are otherwise normal, apart from the hydarthron of the right knee.

Laboratory findings: Hgb. 75—80 %. Blood cholesterol 175 mg per cent. No abnormal granulation of the white blood corpuscles demonstrated. Urine: no abnormality.

Ophthalmological examination: no corneal opacity. The optic discs are grayish-white with blurred margins.

Radiological examination at the sixth admission (1948). The skull is large, broad and brachycephalic (Figs. 8 and 9). The forehead is steep and the back of the head flat. The walls of the skull are very thick, particularly in the mid-line where a prominent ridge is seen at the sagittal suture. No enlargement of the sella turcica. The temporal regions bulge considerably. Hypertelorism is present and the eruption of the teeth delayed.

The ribs are broad and club-shaped. A sinistro-convex scoliosis is noted, particularly in the upper lumbar vertebrae. A marked kyphosis is noted in the lateral view of this region. The second lumbar vertebra is deformed and its upper centre absent.

Upper extremities: The bones are slender (Fig. 10). The metacarpal bones and the phalanges are, however, somewhat quadrate in shape (Fig. 11). The ossification of the carpal bones is slightly delayed.

Fig. 7. Case 2. Claw-like hand.

Lower extremities: The sutures of the pelvis are normal, and the inferior rami have fused. There is pronounced coxa valga (Fig. 12). The trochanteric apophysis is not ossified. The femur, tibia and fibula are slender. A swelling of the soft tissues and of the suprapatellar bursa of the right knee is visible.

The spongy bone network is coarse, the corticalis thin and the calcium content much diminished in all parts of the skeleton except the skull.

It will be seen that none of the cases reported are typical cases of Hurler's syndrome, as they have not all the characteristic signs. Thus they all lack corneal opacity and none of the patients is a dwarf. Only one of them (case no. 2) was deaf and was not, or only insignificantly, mentally backward.

On the other hand they have so many symptoms, particularly enlargement of the liver and spleen, the grotesque appearance and the radiological abnormalities mentioned above that they must in our opinion be classified as atypical forms of Hurler's syndrome.

DE LANGE & WOLTRING have described an atypical form which they call the E type. It differs from the classical form of Hurler's syndrome by the absence of corneal opacity, lumbar kyphosis and enlargement of the sella turcica. One of their patients was not a dwarf and when examined later did not seem to be mentally backward.

Our cases no. 1 and 2 bear a resemblance to the E type, as they are of normal height and have no corneal opacity, but they differ from the E type in having a large sella turcica and a lumbar kyphosis (which, however, was only of a slight nature in case no. 2).

NJÅ has reported a family with 5 cases of a sex-linked recessive form of Hurler's syndrome. The cornea was normal in all cases. Two of them (no. 1 and 5) were of average height. Only one case (no. 1) was thoroughly radiologically examined and had abnormities typical of Hurler's syndrome. In case no. 5 the spinal column only had been radiologically examined, and here the characteristic kyphosis was found, although the ribs were normal. The other cases had not undergone roentgen examination but were clinically typical cases of Hurler's syndrome, except for the absence of corneal opacity.

Fig. 8. Case 3. Thick-walled, large brachycephalic skull with closed sutures.

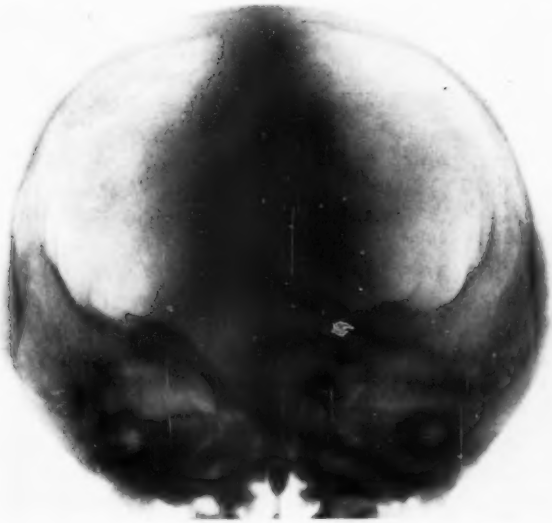


Fig. 9. Case 3. Thick ridge at the sagittal suture. Bulging temporal regions.

Fig. 10. Case 3. Upper extremity: slender bones with halisteresis and coarse bone structure.

Fig. 11. Case 3. Quadrangular-shaped metacarpals with halisteresis and coarse structure.

Our cases no. 1 and 2 are of normal height and they have no corneal opacities. They are both males. But, as no similar cases in their families have been reported and they each only had one brother, it is impossible to show any sex-linked recessive heredity. It thus cannot be proved that they belong to this group.

WIEDEMANN has reported a »late» form of Hurler's syndrome where the first symptoms were observed at the age of 3 years and which bears a close resemblance to Morquio's syndrome. This patient had very small opacities of the corneae, but he was not deaf or mentally backward. The ribs were not broad, and a lumbar lordosis and dorsal kyphosis were

Fig. 12. Case 3. Coxa valga: halisteresis and coarse bone structure.

present. This case differs very much from other cases of Hurler's syndrome.

Our case no. 3 has the following symptoms: Mental backwardness, a grotesque appearance, a large oxy-brachycephalic skull with thick walls, club-shaped ribs and kyphoscoliosis of the upper lumbar spine. For a long period the patient had enlargement of the liver and spleen. The metacarpal bones are somewhat quadrangular. On the other hand the following symptoms are absent: corneal opacity, impaired hearing, dwarfism. The bones of the extremities are slender and halisteretic instead of showing characteristic density. The hands are not plump or the fingers claw-like. The movement of the joints is not limited.

The halisteresis and the slight deformity of the bones of the extremities show that this case cannot belong to one of the types mentioned above.

The structure of the bones together with the thick-walled skull, although without radial striations, might be suggestive of Cooley's anaemia. However, no sickling of the red blood cells could be demonstrated, and this disease is unknown in Denmark.

The thick-walled skull might also suggest hyperostoses following rickets, but this cannot be the explanation in this particular case, since repeated radiological examinations from the age of 9 months never revealed any signs of rickets in other bones.

Caffey describes an osteoporotic type of Hurler's syndrome where the corticalis of the bones of the extremities is thin, and the development of

Fig. 13.

Fig. 13. Hypothyroidism. 3 years old boy. Lumbar kyphosis with defective body of the first lumbar vertebra (arrow).

Fig. 14.

Fig. 14. Chondrodystrophy. 5 years old girl. Lumbar kyphosis with absence of limbus centre of first lumbar vertebra (arrow).

the spongiosa seems to be defective. This description fits in with our case no. 3, and in our opinion this case must be classified in this group.

Differential Diagnosis

Congenital hypothyroidism. In this disease the following symptoms are also present: Disproportionate dwarfism, short thick extremities, short and broad hands, prominent abdomen, a plump face and mental backwardness.

By radiological examination irregularities of the lumbar vertebrae may also be found and the limbus centres absent (Fig. 23). The appearances of the lumbar spine may thus be rather similar to the picture seen in Hurler's syndrome. The bones of the extremities are short and thick, and they may bear a rather close resemblance to those found in atypical

cases of Hurler's syndrome. The eruption of the teeth is delayed, and the closure of the anterior fontanel is retarded.

The most important differences between these two diseases is that in hypothyroidism, enlargement of the liver and spleen is absent, the basal metabolic rate decreased, and the blood cholesterol in most cases increased. By radiological examination the most outstanding feature in hypothyroidism is the delayed ossification of the epiphyses, but this may, according to WASHINGTON, be seen in Hurler's syndrome. It is also present in our three cases, but only to a very slight degree. This contrasts with the great retardation seen in those cases of hypothyroidism where lumbar kyphosis and thickened bones are present.

CAFFEY, NJÅ, NOTTER, WIEDEMANN and other authors have stated that the differential diagnosis between Hurler's syndrome and *Morquio's syndrome* presents difficulties. In this latter disease abnormities of the spinal column are also found, but these are most pronounced in the dorsal region; a severe kyphoscoliosis is usually present. As a rule marked irregularities are seen in the metaphyses. The differences in the clinical picture are also considerable, as the patients are mentally normal and have no enlargement of the liver and spleen, corneal opacity or deafness.

The common (hypoplastic) type of *chondrodystrophy* is in our experience more apt to be confounded with Hurler's syndrome, as the patients of this type are dwarfs with short, thick extremities, broad, short hands and relatively large skulls.

Radiological examination generally discloses a lumbar lordosis, but at times a lumbar kyphosis with absence of limbus centres bearing a rather close resemblance to the findings in Hurler's syndrome may be found (Fig. 14). The bones of the extremities are short, broad and curved, but the metaphyses are as a rule considerably broader than the diaphyses so that a dumb-bell shaped appearance of the bones is produced.

Clinically the patients differ from those with Hurler's syndrome in having normal intelligence, no corneal opacity, deafness, or enlargement of the liver or spleen.

Conclusions

In typical cases of Hurler's syndrome the signs mentioned in the introduction are found. In atypical cases one or more of these signs may be absent, and the bones may be osteoporotic. The most constant signs, however, are: a grotesque appearance with a large head, claw-like hands, enlargement of the liver and spleen, a thick-walled brachycephalic or scaphocephalic skull, broad club-shaped ribs, lumbar kyphosis, and thickened bones of the extremities; in these latter broad diaphyses, coarse bone structure and increased calcium content are found.

Several of these signs must be present, or the disease cannot be diagnosed; any one sign is not sufficient.

SUMMARY

The authors mention the typical signs of Hurler's syndrome and report three atypical cases. Two of the cases showed typical radiological changes. The third case was of the osteoporotic type. None of them had corneal opacity. Two of them showed no signs of deafness either and one had only insignificant mental backwardness.

The authors discuss the differential diagnosis of hypothyroidism and chondrodystrophy.

ZUSAMMENFASSUNG

Die Autoren besprechen die typischen Kennzeichen des Hurlerschen Syndroms und berichten über drei atypische Fälle. Zwei von diesen Fällen zeigten typische radiologische Veränderungen. Der dritte Fall gehörte zum osteoporotischen Typ. Keiner von ihnen hatte Hornhaut-Trübungen. Zwei von ihnen zeigten auch keine Zeichen von Taubheit, und bei einem fand sich nur unbedeutende geistige Schwäche.

Der Autor bespricht die Differential-Diagnose von Hypothyroideismus und Chondrodystrophie.

RÉSUMÉ

Les auteurs mentionnent les caractéristiques du syndrome de Hurler et relatent 3 cas atypiques. Deux de ceux-ci donnèrent une radiographie typique. Le troisième était du type ostéoporotique. Aucun ne présentait de l'opacité de la cornée. Deux d'entre eux n'avaient aucun signe de surdité non plus, et l'un n'avait qu'un léger engourdissement mental.

Les auteurs discutent le diagnostic en vue de le différentier de celui de l'hypothyroïdisme et de la chondrodystrophie.

REFERENCES

Caffey, J.: Pediatric X-Ray Diagnosis. Chicago 1945.

Gasser, C. & Zellweger, H.: Report to the 6th International Congress of Pediatrics, Zürich 1950.

Hurler, G.: Zschr. f. Kinderh., 24 (1919), 220.

Kressler, R. J. & Aegerter, E. E.: J. Pediat., 12 (1938), 579.

de Lange, C., Gerlings, P. G., de Kleyn, A., & Letting, T. W.: Acta paediat., 31 (1944), 398.

de Lange, C. & Woltring, L.: Acta paediat. 19 (1937), 71.

Njå, A.: Acta paediat., 33 (1946), 267.

Notter, G.: Acta radiol., 32 (1949), 439.

v. Pfaundler, M.: Jahrb. f. Kinderh., 92 (1920), 420.

Washington, J. A.: Lipochondrodystrophy, in Brennemann, J. (Ed.): Practice of Pediatrics (Hagerstown, Md.: W. F. Prior, Inc., 1937), Vol. IV, Chap. 30.

Wiedemann, H.-R.: Helvet. Paediat. acta, 4 (1949), 77.

DEPARTMENT FOR CELL RESEARCH AND GENETICS, KAROLINSKA INSTITUTET, STOCKHOLM, SWEDEN.

EQUIPMENT FOR MICRORADIOGRAPHY WITH SOFT ROENTGEN RAYS[1]

by

A. Engström and *L. Wegstedt*

Introduction

Qualitative and quantitative microradiography has proven to be useful methods in histo- and cytochemistry (cf. ENGSTRÖM 1950). Particularly in the investigation of hard tissues such as bone tissue and other dense and roentgen ray absorbing biological tissues a simplified technique may be used. For the investigation of smears of mammalian cells etc. soft roentgen rays coupled with investigation in vacuum are necessary but for tissues having high roentgen ray contrast roentgen rays which are more penetrating can be used.

This paper describes the construction of microradiographic equipment for both qualitative and quantitative microradiography of dense biological tissues using a commercial sealed off roentgen tube.

Principle

The specimen, which is to be examined is placed in good contact with a very fine grained photographic emulsion (Lippmann-film, Eastman Kodak Spectroscopic Plate 548 or 649). Using soft roentgen rays a contact image of the sample is produced, cf. fig. 1. The small roentgen image is then enlarged by photomicrography. The resolving power of the technique depends upon the granularity of the film and the geometrical arrangement of roentgen ray source, sample and film. The fine grained film emulsions are capable of a resolution of less than 1 μ in thin objects with good contrast. The geometrical unsharpness in the image can be seen from fig. 2. The blurring of a point, *e. g.* at the surface of a

[1] Submitted for publication, Jan. 15, 1951.

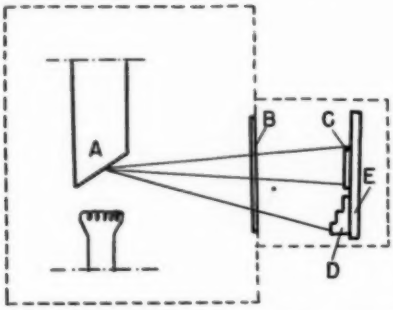


Fig. 1. Arrangement for microradiography.
A, target of the roentgen tube.
B, filter (window).
C, sample.
D, reference system.
E, photographic film.

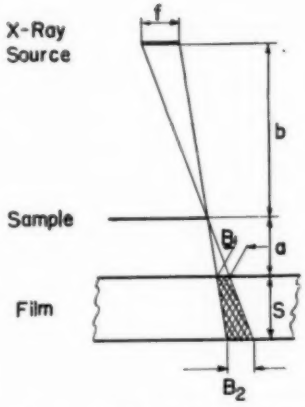


Fig. 2. Blurring in the microradiogram.

sample at the distance a from the film emulsion and at a distance b from the roentgen ray source is,

$$B_1 = \frac{f \cdot a}{b}$$

where f is the magnitude of the focal spot. If the photographic film emulsion has the thickness s and the roentgen rays penetrate the whole emulsion the blurring will be,

$$B_2 = \frac{f \cdot (a + s)}{b}$$

With a focus size of 5 mm a target to film distance of 5 cm the blurring for the surface of a 10 μ thick sample in close contact with a thin emulsion is 1 μ. For thinner samples better resolution can be expected.

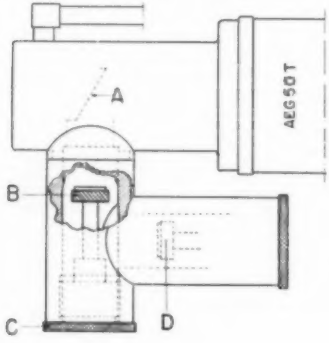


Fig. 3. The roentgen tube and sample holder.
A, target of the roentgen tube.
B, sample holder in position for direct microradiography and D position for microradiography with secondary roentgen rays.
C, locking screw.

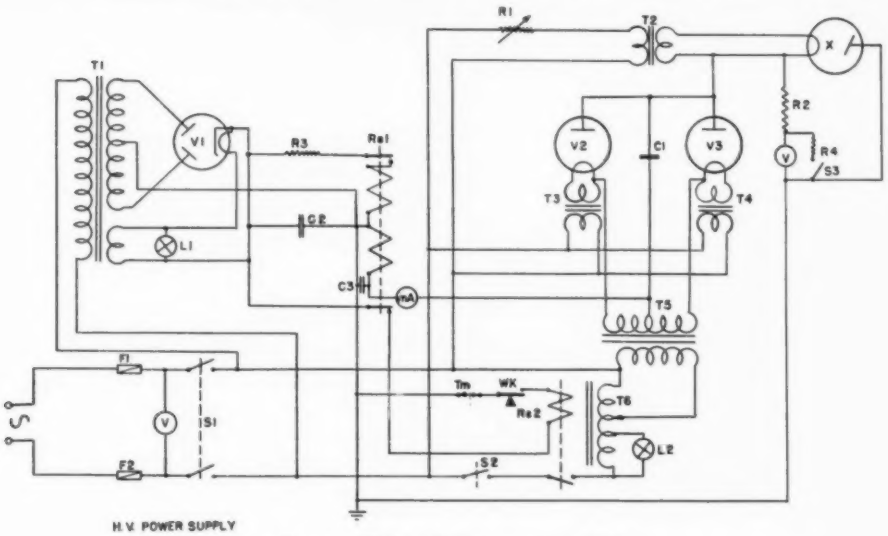


Fig. 4. High voltage power supply.

C 1 0.3 μF 15 kV wV
C 2 16 μF 450 V »
C 3 25 μF 25 V »

F 1, F 2 Fuses 6 A

L 1, L 2 Pilot lamps

mA mA meter 0—50 mA

R 1 Rheostat 750 Ω 50 w
R 2 10 Meg Ω 40 w
R 3 1 k Ω 2 w mA
R 4 45 Ω

Re1 Relay winding 1 40 mA
winding 2 locking winding.

Re2 Hg-relay manoeuvre voltage 110 V=
breaking capacity 6 A 250 V

S 1 Toggle switch 6 A 250 V
S 2 » » 6 A 250 V
S 3 » »

T 1 Transformer prim. 220 V 50 c/s sec
2 × 125 V 10 mA 6.3 V 1 A
T 2 Transformer prim. 220 V 50 c/s sec.
7 V 6 A Isol. for 30 kV
T 3 Transformer prim. 220 V 50 c/s sec.
2.5 V 5 A Isol. for 30 kV
T 4 Transformer prim. 220 V 50 c/s sec.
2.5 V 5 A Isol. for 30 kV
T 5 Transformer prim. 220 V 50 c/s sec.
2 × 9.7 kV r. m. s. 40 mA D. C.
Isol. for 40 kV
T 6 Variable transformer prim. 220 V 50
c/s sec. 0—220 V 1kVA

Tm Connections for timing device.

V Voltmeters

V1 6 X 5

V2 V3 8013

Wk Coaling water relay.

X Roentgen tube.

In order to measure quantitatively the roentgen ray absorption in small parts of the microradiogram a step wedge system is simultaneously exposed with the sample. Knowing the properties of the step wedge the absorption in different points in the sample can be calculated when comparing the density from a structure in the microradiogram with that of the step wedge.

Roentgen Tube and High Voltage Unit

As the roentgen ray source a Machlett roentgen tube type AEG 50 was chosen (Cf. ROGERS 1947). The tube has relatively good output of soft roentgen rays up to about 4 Å. The inherent filtration is about 1 mm Be. The tube was provided with a sample holder according to fig. 3. The sample is mounted on the sample holder together with the reference system and pressed into good contact with the fine grained photographic film. The voltage applied to the tube depends on the nature of the sample.

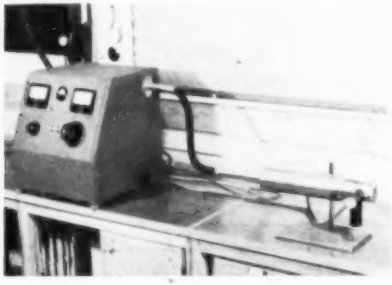
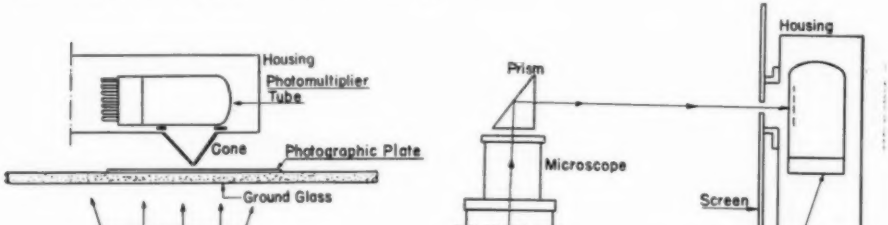


Fig. 5. H. V. unit and roentgen tube with sample holder.

Sometimes it is desired to expose the sample with characteristic secondary radiation. This can be affected by placing a secondary radiator at the place of the sample and mounting the sample-film at right angles to the direction of the primary beam.

The roentgen tube was supplied with high voltage (H. V.) from a special unit giving well smoothed current up to a voltage of about 15 kV. The circuit for the H. V. unit is shown in fig. 4. together with the list of materials. As can be seen from fig. 4. the unit is supplied with relays which secure safe running conditions. The flow of water controls a relay which breaks the main current when the water pressure falls below a certain value. When the master switch is connected a delay relay effects that it takes some time before the H. V. can be switched on. The delayed action depends upon the time necessary for an indirectly heated rectifier tube to come into function. A timing unit can be connected to the H. V. unit. A photograph of the roentgen tube with the H. V. power supply is shown in fig. 5.



a) b)

Fig. 6. a) Arrangement for photometry of plates.
b) Arrangement for direct photometry of the microradiograms.

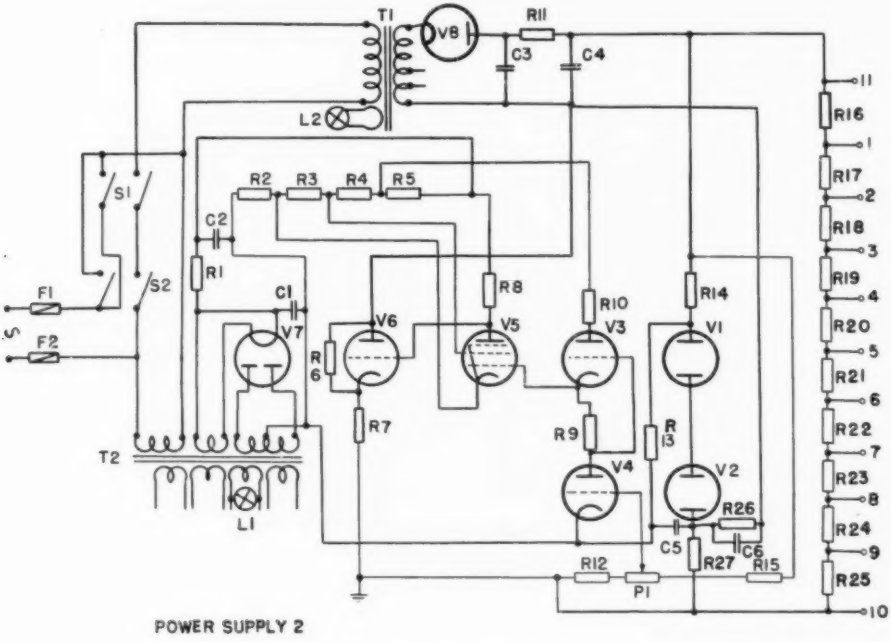


Fig. 7. Power supply for photomultiplier tube.

C 1, C 2 4 μF 600 V wV
C 3, C 4 2 μF 2,000 V »
C 5 2 μF 500 V »
C 6 0.2 μF 1,000 V »

F 1, F 2 Fuses 2 A

L 1, L 2 Pilot lights 6 V

P 1 Potentiometer 50 k Ω

R 1 15 k Ω 2 w
R 2, R 3, R 4 parts of one resistor of 10 k Ω 12 w with adjustable lugs.
R 5 20 k Ω 12 w
R 6 10 M Ω 2 w
R 7 3 k Ω 1 w
R 8 200 k Ω 1 w
R 9 2 k Ω 1/4 w
R 10 4 k Ω 1/4 w
R 11 50 k Ω 2 w
R 12 200 k Ω 2 w
R 13 50 k Ω 0.5 w
R 14 210 k Ω 6 w (3 st 70 k Ω 2 w)
R 15 800 k Ω 8 w (4 st 200 k Ω 2 w)
R 16—R 25 50 k Ω 1 w
R 26 500 k Ω
R 27 400 Ω

S 1, S 2 Toggle switches

T 1 Transformer prim. 220 V 50 c/s sec. 1,400 V 10 mA = 6.5 V 0.5 A
T 2 Transformer prim. 220 V 50 c/s sec. 2 × 350 V 25 mA 5 V 2 A 6.3 V 3 A 6.3 V 0.6 A 6.3 V 0.3 A 2.5 V 2 A

V 1, V 2 85 A 1
V 3, V 4 ECC 40
V 5 EF 40
V 6 HK 24
V 7 5 Y 3

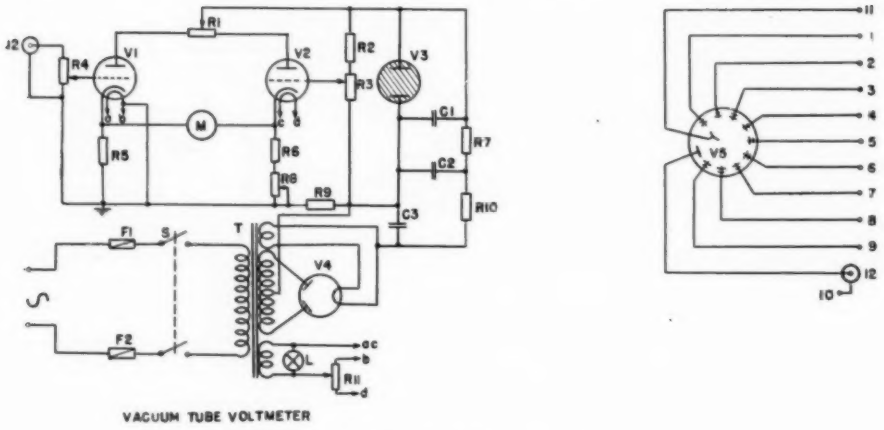


Fig. 8. Electronic tube voltmeter.

C 1 0.1 μF 600 V wV
C 2, C 3 2 μF 600 V wV
F 1, F 2 Fuses 2 A
L Pilot lamp
M mA meter 0—1 mA Ri = 200 Ω
R 1 2 k Ω pot.
R 2 150 k Ω 1 w
R 3 2 k Ω pot.
R 4 2 M Ω pot.
R 5 1.5 k Ω 1 w
R 6 1.2 k Ω 1 w
R 7 7 k Ω 2 w
R 8 600 Ω pot.
R 9 100 Ω 1 w
R 10 7 k Ω 2 w
R 11 6 Ω 7 w
S Toggle switch
T Transformer prim. 220 V 50 c/s sec. 2 × 350 V 30 mA 5 V 2 A 6.3 V 0.6 A
V 1, V 2 EBC 11
V 3 OA 2
V 4 5 Y 3
V 5 931 A

Photometer

There are two ways of measuring the absorption of roentgen rays via the small microradiograms. One is to employ a microscope to magnify the microradiogram and then compare the light intensities in the image of the microradiogram of the sample and wedge system.

The other way is to make a photomicrograph of both the microradiogram and wedge system and then compare the densities for the sample and wedge system in the photomicrograph. In this case the photometer can be of simpler construction. The photometer constructed and described in the following can be used for both types of investigation.

The light sensitive part, a photomultiplier tube, is mounted in a small housing with a shutter. When measuring the density of ordinary photographic plates (magnifications of microradiograms) a small pinhole is

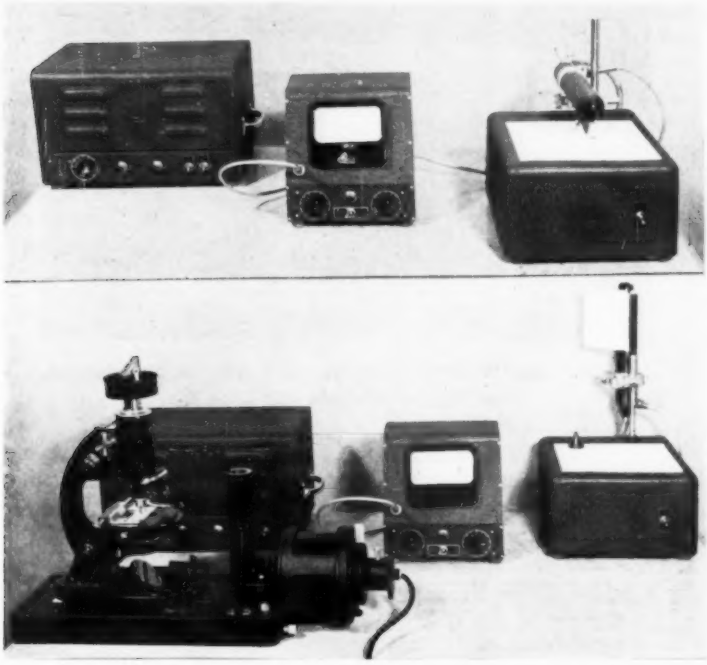


Fig. 9 a.

Fig. 9 b.

Fig. 9. Photographs of the photometer.
a) for photometry of plates. b) for photometry of microradiograms.

placed over the light sensitive part of the photomultiplier tube according to fig. 6 a. It is necessary to collect light at a certain angle if the light incident to the plate is parallel. If diffuse light is used for the illumination of the photographic plate a smaller aperture can be used. As is shown in fig. 6 a an illumination box, which was fed from a storage battery, was used as the light source. This box also served as a viewing box for the plates. The cone applied to the photomultiplier serves as a pointer under which the photographic plate can be moved, thus securing exact localization of the area for photometric analysis. During the course of one series of measurement the inherent positions between photomultiplier and illumination box must not be changed.

The photomultiplier tube is supplied by voltage from equipment shown in fig. 7, which gives well stabilized voltage. The resistors must be selected in such a way that their temperature and temperature coefficients match with the gaseous voltage stabilizing tubes. Carefully selec-

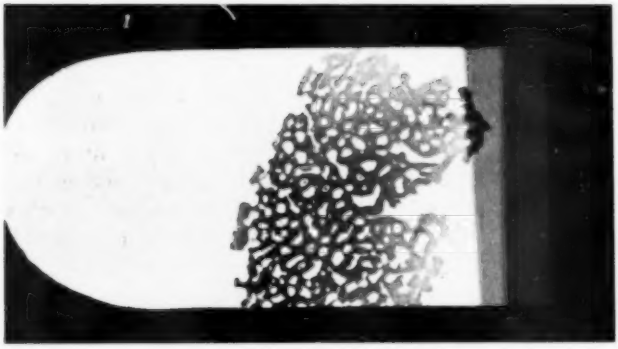


Fig. 10. Low power photograph of a microradiogram with sample and reference system 5 ×.

ted material gives a voltage stable to 1 ‰. About 90 volts is used on each dynode in the photo tube. The anode current from the photomultiplier is measured by an electronic voltmeter, the diagram of which is shown in fig. 8. The complete unit for photometry of plates is shown in fig. 9 a.

Using a microscope direct photometry of the small roentgen film is possible. According to fig. 6 b the cone for collection of light is replaced by a screen with a pinhole. By a prism the microscope image of the microradiogram is projected on the white screen with the pinhole. By moving the mechanical stage of the microscope different areas of the microradiogram can be projected over the pinhole and the light absorption measured. Fig. 9 b shows the use of the photometer for direct measurements of the light absorption in the microradiogram. Aperture conditions of the microscope condenser and objective must be properly selected and the homogeneity of the area in the field under photometric analysis must be as good as possible before valid measurements can be obtained.

Applications and Discussions

As mentioned in the introduction the Machlett AEG 50 roentgen tube gives soft roentgen rays up to a wavelength of about 4 Å. Microradiography of thin sections of ordinary biological tissue requires still softer roentgen rays in order to obtain adequate contrast. The equipment described in this paper has successfully been used for microradiography of bone tissue and other structures with a high content of calcium salts. Also in soft tissues with a high content of dry substance, such as the outer layers of skin, the apparatus gives enough contrast for relatively

thin objects. Microtome sections of soft tissues which have been impregnated with salt of heavy metals, »roentgen ray staining», have been successfully microradiographed.

In fig. 10 is shown a low power magnification of a ground section of bone together with its reference system. When evaluating the absorption of roentgen rays in the sample first the photometer deflection for different steps in the wedge are plotted against either the weight in grams/cm² or the number of the steps in the wedge. Then, when measuring the photographic density (photometer deflection) of the special structure under investigation, the curve obtained (fig. 11) can be used to express the absorption of the sample in terms of the reference system. Thus the relative absorption is obtained and the absolute values are obtained when the absorption of the wedge is calibrated in macroscale for the same type of roentgen rays and under identical conditions under which the microradiogram was registered. The calibration is easiest performed using a Geiger-counter or ionization chamber to measure the different roentgen ray intensities.

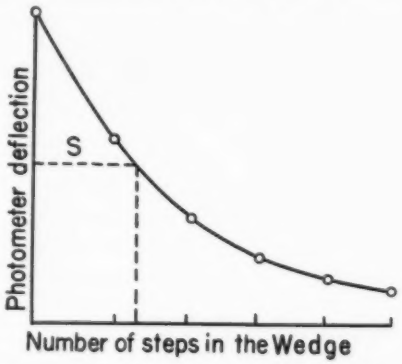
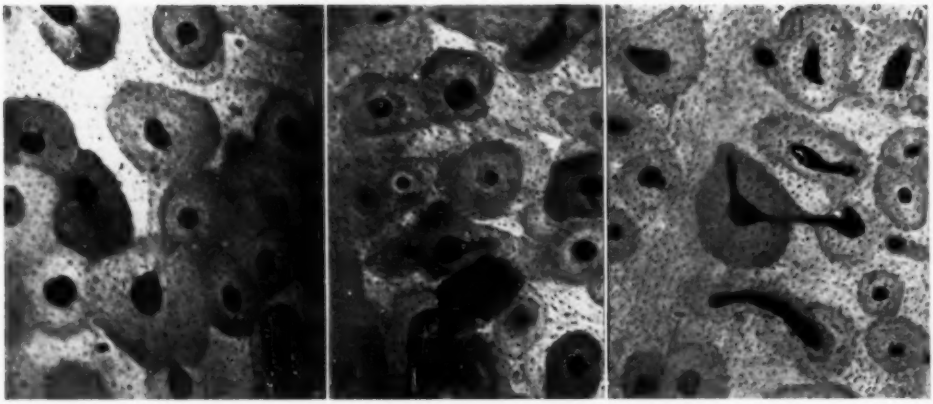


Fig. 11. The photometer deflection versus the number of steps in the wedge. The dotted line indicates the photometer deflection for a certain structure.

In fig. 12 is shown a photomicrograph of a cross section of bone tissue and the different distribution of mineral salts is well demonstrated. The picture is taken with 6 kV. If the bone section is decalcified and again exposed for the same time with the same type of roentgen rays no contrast at all is obtained. Therefore the microradiogram shows the distribution of mineral salts in the section and quantitative measurements give the relative and absolute distribution of calcium salts. *The method thus allows the determination of total amounts of mineral salts in small volumes of bone tissue.*

Experiments to apply the method to sections of *e. g.* liver tissue cut at 5—10 μ were not successful even if the roentgen tube was run with a voltage as low as 3 kV. In this case the short wavelength limit of the continuous roentgen ray spectrum is about 4 Å. Wavelengths longer than 4 Å would be suitable for thin sections of soft tissues. However, even if there were possibilities of obtaining roentgen rays of wavelengths > 4 Å with the AEG 50 tube, the enormously long exposure times required makes it almost impossible to use the apparatus for such



a. b. c.

Fig. 12. Microradiograms of bone tissue. Ground sections, about 30 μ thick from a) ulna, ♂ 45 years of age, b) femur, ♀ 73 years, c) metacarpus, horse. The areas, which are white are more dense to roentgen rays than the black. The osteocytes are clearly seen in the picture. Haversian systems, secondary bone, has less content of mineral salts than primary bone and very old secondary bone. In b) the edge of a resorption cavity is quite sharp. Magnification about 80 times.

purposes. The fine grained film to be used, *e. g.* Lippman film is about 10,000 times less sensitive than ordinary roentgen film.

Summarizing the use of a sealed off roentgen tube with beryllium window for microradiography of biological material the following conclusions can be drawn:

1. The AEG 50 beryllium window roentgen tube is a tube of relatively simple usage for microradiography of certain biological materials.

2. Biological tissues, containing high amounts of elements giving good roentgen contrast, such as bone tissue, can be examined in thin sections. The apparatus has been of great value in investigating the distribution of mineral salts in bone tissue under normal and certain pathological conditions (*e. g.* AMPRINO and ENGSTRÖM 1950).

3. Thick sections (50—100 μ) of ordinary biological tissues can be examined.

4. The distribution of substances of high roentgen ray absorbing power, *e. g.* materials injected for roentgen contrast, can be examined in thin microtome sections.

5. Microtome sections which have been stained with salts of heavy metals, *e. g.* silver impregnation, staining with phosphotungstic acid can be examined. Areas having the capacity of binding heavy ions can thus be localized.

6. Investigating thin sections requires softer roentgen rays than those which can be obtained from the roentgen tube in the apparatus described in this paper. For this purpose *e. g.* the tube described by ENGSTRÖM and LINDSTRÖM 1950 for the determination of the weight of cells and cell-structures has to be used.

7. The high voltage unit described can be used to supply any tube with a voltage of up to 15 kV.

SUMMARY

Specialized equipment for microradiography is described. The roentgen tube used, Machlett AEG 50, permits the microradiography of certain biological materials with good contrast. The apparatus is especially useful in investigating thin sections of *e. g.* bone or dentine tissue. A photometer for macro- and microscale is also described. Some applications are given and other possible uses of the apparatus suggested.

ZUSAMMENFASSUNG

Eine Spezial-Ausrüstung für Mikroradiographie wird beschrieben. Die dabei verwendete Röntgenröhre, Machlett AEG 50, gestattet die kontrastreiche Mikroradiographie gewisser biologischer Stoffe. Die Apparatur ist besonders brauchbar zur Untersuchung dünner Schnitte von z. B. Knochen oder dentalem Gewebe. Ein Photometer für Makro- und Mikromessungen wird ebenfalls beschrieben. Einige bereits erfolgte Verwendungen werden mitgeteilt und andere Anwendungsmöglichkeiten der Apparatur vorgeschlagen.

RÉSUMÉ

Un équipement spécial pour microradiographie est décrit. Le tube Roentgen utilisé, Machlett AEG 50, permet la microradiographie de certaines matières biologiques et donne une bonne image. L'appareil est spécialement utile lors de l'investigation des coupes minces d'os par exemple ou de tissu dentaire. Un photomètre à l'échelle macroscopique et microscopique est également décrit. Quelques applications de l'appareil sont présentées et d'autres possibles sont suggérées.

REFERENCES

AMPRINO, R. and ENGSTRÖM, A.: Experientia VI/7 (1950), 267.

ENGSTRÖM, A.: In Progress in Biophysics and Biophysical Chemistry. Ed. by Butler and Randall, Butterworths Publ. Co. London 1950.

ENGSTRÖM, A. and LINDSTRÖM, B.: Biochem. et Biophys. Acta 4 (1950), 351.

ROGERS, T. H.: Radiology 48 (1947), 594.

FROM THE INSTITUTE OF PATHOLOGY, OSLO UNIVERSITY, NORWAY

OBSERVATIONS ON THE SKIN REACTION TO THE SUBCUTANEOUS APPLICATION OF METALLIC POLONIUM IN MICE[1]

by

Leiv Kreyberg and *Finn Devik*

One of us (DEVIK 1951) has in another publication described changes in the epidermis and adjacent tissues, following external irradiation by a 10 mm × 10 mm nickel plate covered with 10 millicuries polonium. One of the problems raised in those experiments was the relationship between the cell damage and cell reaction caused by the *direct* action of the alpha particles, and the changes caused *via the tissue fluids, blood vessels* and by *other less known factors.*

As a counterpart to those experiments, the following investigation was carried out: The same nickel-polonium plate was introduced through an incision under the whole skin in a series of mice, the plate being held in position for a period varying from 20 seconds to 30 minutes, the polonium-covered side facing the epidermis and in actual contact with the loose connective tissue covering the panniculus carnosus. The activity of the polonium preparation was, in this case, about 5 millicuries. The same strain of hairless mice, 23 in all, was used as in the previous experiment. It was soon evident that an appreciable amount of polonium was dissolved in the tissue fluid during the period of exposure. Most of the animals developed marked signs of radiation-sickness: asthenia, anemia and loss of body fluid and weight.

Of the 23 animals 5 died on the 6th, 7th, 10th, 10th, and 40th day respectively after the operation, 13 animals were killed for histological examination after a short period after the operation, and 5 were killed after 12 to 26 days exposure.

At autopsy the spleen constantly showed a marked or extreme atrophy (Fig. 7), and the bone marrow was often found to be in a gelatinous con-

[1] Submitted for publication, Febr. 3, 1951.

Figs. 1—3. Mouse $^{13}/_{1}$ 50. The nickel-polonium plate had been applied for 15 minutes, and the animal sacrificed 24 hours later.

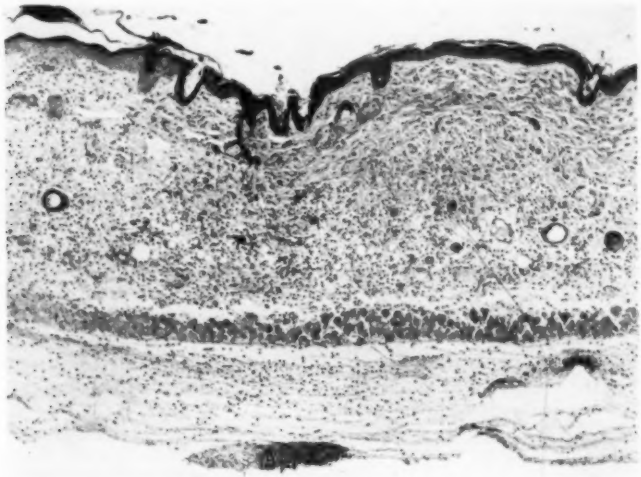


Fig. 1. The histological reaction in the skin. Hematoxylin-Eosin. × 60.

Fig. 2.

Fig. 3.

Fig. 2. Radioautograph of the skin. Two sections. × 5.
Fig. 3 a. Spleen. Histological section. Hematoxylin-Eosin. ×5.
Fig. 3 b. The same spleen. Radioautograph. × 5.

dition. Autoradiographs showed a considerable accumulation of radioactive material in the central organs of the reticulo-endothelial system, as well as in the kidneys. Radioactive material, corresponding to the bed of the nickel-polonium plate, was found in the whole thickness of the skin. See figures.

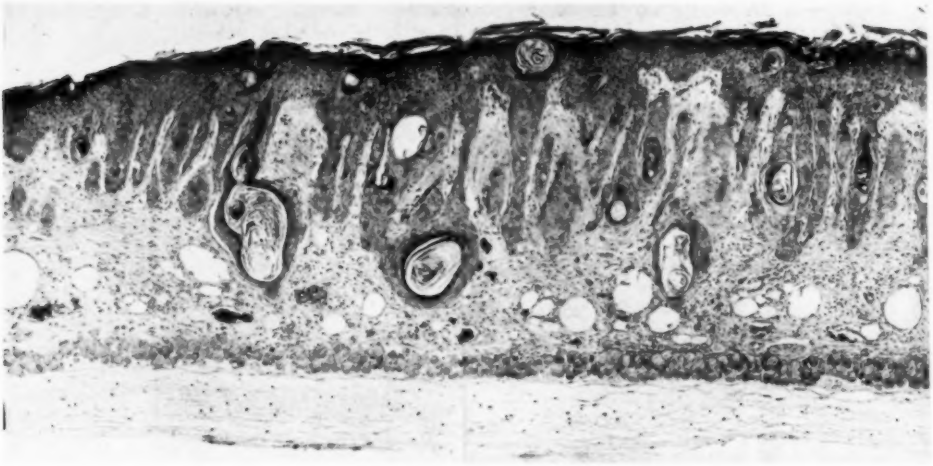


Fig. 4. Mouse $^{21}/_{1}$ 50. Skin section showing a very marked hyperplasia and a moderate inflammation. The nickel-polonium plate had been applied for 20 seconds and the animal sacrificed 16 days later. Hematoxylin-Eosin. × 60.

Protocols.

Mouse $^{13}/_{1}$ 50 was exposed to the nickel-polonium plate under the skin for 15 minutes, and killed 24 hours later. At that moment the skin showed a very marked localized edema with some hyperemia, the edges of which presented somewhat blurred outlines.

Histological sections (Fig. 1) showed marked edema, especially under the panniculus carnosus, corresponding to the tissue which had been in direct contact with the polonium. In the whole thickness of the skin a considerable invasion of leucocytes could be seen. Radioautograph showed heavy deposits of radioactive material (Fig. 2). Polonium was also found in quantities in the spleen. (Fig. 3 a and b.)

Mouse $^{21}/_{1}$ 50 was exposed to the nickel-polonium plate for 20 seconds and killed 16 days later. The first day after the operation a slight hyperemia could be observed, but no edema. From the fifth day edema appeared, the edema increasing day by day, becoming harder and more sharply defined. On the sixteenth day the skin was hard, elevated and had a glossy surface. The general condition of the animal was good.

Histological sections of the skin (Fig. 4) revealed marked thickening of the epidermis. The hair follicles had increased in size and grown deep into the corium, forming thick strands with keratin pearls. A number of the epithelial cells showed monstrous nuclei, abnormal mitoses, micro-nuclei and swollen and vacuolized cytoplasm. There was considerable edema in the connective tissue. There were few cells between the hair follicles in the stroma, but in the deeper layers some leucocytes could be observed.

Mouse $^{19}/_{1}$ 50 was exposed to the nickel-polonium plate for 2 minutes and killed 26 days later. The second day after the operation a light hyperemia and edema was observed. The edema increased after a week and was at first not sharply limited.

On the eleventh day the exposed field was hard and a necrotic area appeared in the centre. On the twenty-fifth day a hard, thick disc, 15 mm in diameter, could be seen and felt, the centre still being necrotic. An unusual vascular reaction was seen around the necrotic area, and radiating ectatic vessels with a very sluggish circulation were noted (Fig. 5). After intra-peritoneal injection of fluorescein the animal turned marked yellow in the course of 1—2 minutes. The ectatic vessels remained unstained. The general condition of the animal was poor, the skin pale, dry and shrunken.

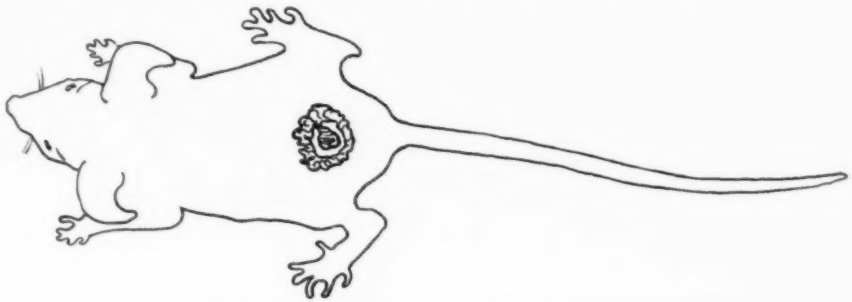


Fig. 5. Mouse $^{19}/_{1}$ 50. Appearance of skin lesion. See text.

Histological sections from the skin (Fig. 6) showed, peripheral to the necrotic area, a marked thickening of the epidermis with deep infiltration of the large and hypertrophied hair-follicles with large keratin pearls, giving a picture strongly resembling early carcinoma. A number of the epithelial cells showed the same atypical features as described under Mouse $^{21}/_{1}$ 50. The connective tissue was edematous with few cells present, except in the areas with local necrosis and leucocyte reaction. Radioautographs of the skin of the kidneys and of the very small, atrophic spleen (Fig. 7 b) showed considerable deposits of radioactive material.

The marked hyperplastic reaction of the epidermis and the hair-follicles described above, presented a picture not unlike that seen in early tar carcinomas. Metastases were not observed and homotransplantation was not successful. A transplantation was performed the 29th day after operation (Mouse $^{20}/_{1}$ 50), the host dying suddenly 11 days after transplantation. The transplant was healthy-looking, but did not show evidence of active growth. This transplantation experiment is, however, not at all conclusive.

Regarding exposure to alpha particles, the *external type of irradiation* at distance limits the effect nearly exclusively to the epidermis. A small dose only, may effect the superficial layers of the corium. The general condition is not affected. Finally, the radiation effect is limited in time to the period of direct exposure.

The *internal application* of polonium, even for a very brief period, leads to a transfer of some of the metal to the tissue fluid. From this fluid, some of the dissolved polonium is carried by the blood stream to distant

Figs. 6—7. Mouse $^{19}/_{1}$ 50. The nickel-polonium plate had been applied for 2 minutes and the animal sacrificed 25 days later.

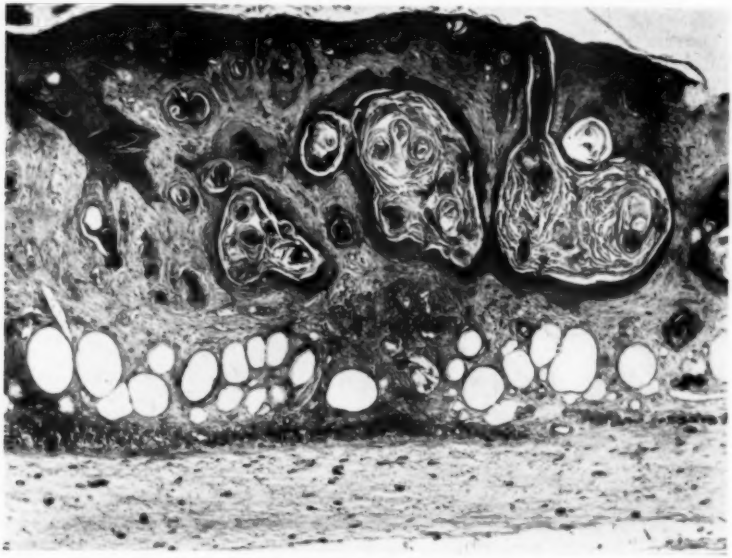


Fig. 6. Histological reaction in the skin. Hematoxylin-Eosin. × 60.

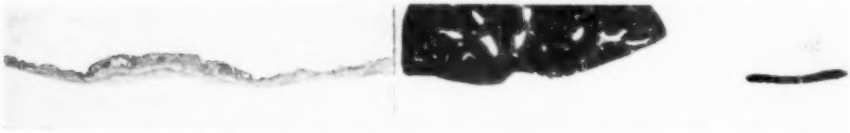


Fig. 7 a. Histological sections of skin, liver and spleen. Hematoxylin-Eosin. × 4.

Fig. 7 b. Radioautographs of the same sections: skin, liver, spleen. × 4.

organs, deposited in the reticulo-endothelial system, or excreted through the kidneys. Some of the polonium follows the local tissue fluid towards the surface of the skin; by radioautographs, one may trace the alpha corpuscles in the connective tissue all the way up to, as they penetrate the epidermis. The irradiation is thereby not limited to a thin layer

of tissue, or a certain part of the skin, but it effects the whole thickness of the skin. Further, in this experiment the effect is not only local, but superimposed upon a general effect; and finally, the exposure is continuous up to the death of the animal.

From these facts, it is evident that it is very difficult to make any definite comparison as to the mechanism of the damage and the repair in the mouse skin in the two series. There is, however, a remarkable difference in the reaction, not least in the epidermis.

In both series the epidermis shows marked signs of radiation damage, manifested by the occurrence of monstrous nuclei, abnormal mitoses, micro-nuclei, vacuolisation and pycnosis. In the series with external application alone, these signs of radiation damage were of less than six days duration. In our present series, the characteristic picture of radiation damage in the epithelium was observed up to the time of the death of the animal, including the mouse killed 40 days after operation. These more prolonged manifestations of direct cell damage may be explained as the effect of the continuous irradiation.

This means that the picture of direct radiation damage is similar in the two series, the main difference consisting in the duration of the morphologic changes. In DEVIK's series, with a brief single external exposure, the changes could be followed for a period of less than a week. In our present series the changes could be followed as long as the exposure lasted, viz. as long as alpha particles were present in the skin.

In addition to these, in principle, similar changes, another sequence of reactions may be noted, showing considerable differences in the two series.

Firstly: In the series with external application, the stroma-vascular reaction is very slight and transient. The series with subcutaneous application shows, however, a very strong and marked stroma-vascular reaction.

Secondly: The series with external application shows slight *atrophy*, of the epithelium lasting for weeks and months in addition to the characteristic picture of radiation damage. In the series with subcutaneous application, on the other hand, the radiation damage is accompanied by a marked *hyperplastic reaction*.

We do not wish to draw any definite *conclusions* from these experiments, our main object being to present a group of facts, but the evidence suggests that the changes in the stroma may represent an important causal factor in the development of the hyperplasia of the epidermis and the hair-follicles. The direct epithelial damage from the irradiation has in DEVIK's experiments evidently not been a sufficient cause for excessive proliferation of the epithelium.

SUMMARY

A nickel plate covered by polonium was introduced under the skin in a series of mice. Some of the polonium was dissolved in the tissue fluid and caused general and local radiation damage. The local changes are described in some detail, and the mechanism of the very marked hyperplasia is discussed. The evidence in favour of the existence of an indirect effect through the connective vascular system is stressed.

ZUSAMMENFASSUNG

Eine mit Polonium überzogene Nickel-Platte wurde einer Reihe von Mäusen unter die Haut geschoben. Geringe Mengen von Polonium lösten sich in der Gewebsflüssigkeit auf und verursachten allgemeine und örtliche Strahlen-Schädigung. Die örtlichen Veränderungen werden in gewissen Einzelheiten beschrieben und der Mechanismus der deutlich gekennzeichneten Hyperplasie besprochen. Auf das wahrscheinliche Vorliegen eines indirekten Effektes auf dem Wege durch das verbindende Gefäss-System wird hingewiesen.

RÉSUMÉ

Une feuille de nickel recouverte de polonium a été introduite sous la peau chez une série de souris. Une partie du polonium a été dissoute par le liquide tissulaire et causait ainsi des dommages généraux et locaux dus à la radiation. Les altérations locales sont décrites à divers points de vue, et le mécanisme de l'importante hyperplasie est discuté. Les preuves à l'appui de l'existence d'un effet indirect par la voie du système vasculaire conjonctif sont mises en valeur.

REFERENCES

DEVIK, F.: Histological and cytological changes produced by alpha-particles in the skin of mice. Acta radiol. 35 (1951), 149.

FROM THE ROENTGEN DEPARTMENT (DIRECTOR: G. FR. PETERSEN) OF THE STATE HOSPITAL, REYKJAVIK, ICELAND

PYELO-URETERITIS CYSTICA[1]

by

G. Fr. Petersen

The object of this paper is to report 2 cases of pyelo-ureteritis cystica presenting characteristic excretory pyelographic appearances. The diagnosis was made after nephrectomy and partial ureterectomy and verified histologically in the first case and in the second it was based on pyelography alone.

The disease was first described by MORGAGNI in 1761. It is rather rare but is occasionally found at operation and autopsy. MORSE (1928) gave sixty literary references of cases of pyelitis, ureteritis and cystitis cystica. PESSIN (1939) found some 85—90 cases reported. During the past few years a considerable number of cases have been described and the disease is probably more common than the literature indicates. LUBARSCH found four cases of ureteritis cystica in 3,000 cases examined, and PESSIN seven in 1,590 necropsies. Cystitis cystica is not a particularly rare condition.

As regards etiology and genesis most authors consider that the cysts arise form epithelial cell nests (LIMBECK-BRUNN) or from occluded mucosal crypts or glands (cystitis glandularis). Histological examinations show that epithelial aberrancy in the ureteral mucosa is common in persons past middle age, but opinions as to genesis differ. Metaplasia with eventual malignant degeneration (PATCH, STERLING, WILSON) has been considered. PATCH and BOTHE and CRISTOL believe in equal sex incidence, and others (LUBARSCH, PESSIN) state that it is more common in females.

The clinical diagnosis is based on cystoscopy and pyelography. JOELSON and JACOBY each diagnosed a case by pyelography in 1929. PATCH (1938) was able to collect 8 clinical cases from the literature and

[1] Paper read at the Sixth International Congress of Radiology in London, July 1950; submitted for publication, Jan. 15, 1951.

added 2 of his own. ARDUINO (1946) mentions 20 cases. I have encountered some 30 cases in the literature.

Symptoms and Signs

If the cysts in the upper urinary tract be few in number and of small size, they may often present no signs. The condition under these circumstances is an unexpected finding at necropsy.

The clinical signs of pyelo-ureteritis cystica are not pathognomonic of the condition. Most authors consider that the underlying cause is a chronic urinary infection of which there is usually evidence. Haematuria is frequently present. Rupture of the cysts is generally thought to be the cause of bleeding, which can be either slight or profuse. If other reasons for the haemorrhage have been ruled out, cyst formations should be carefully sought by cystoscopy and pyelography. Pain in the loin is a common symptom. Stones are often present. Large solitary cysts or clusters of smaller cysts sometimes cause narrowing or even occlusion of the ureter, usually in its upper part, eventually resulting in hydronephrosis.

Diagnosis

Clinical diagnosis is based on excretory or retrograde pyelography, or a combination of the two. The cysts may be localized in the renal pelvis, calyces, ureter or bladder. They are more common in the upper part of the ureter. The cysts may vary in size from under 1 mm up to 2 cm or over in diameter. They are either scattered and solitary, or in the upper part of the ureter and renal pelvis may lie in clusters. The condition is sometimes unilateral.

It is obvious that the roentgen appearances may vary considerably depending on the localization, distribution and size of the cysts. However, the urograms are characteristic and may probably be considered pathognomonic of the condition. Solitary cysts present punched-out oval or rounded filling defects in the contrast medium in the pyelogram, sometimes causing the outline to be irregular or ragged. It is most important to take films with such an amount of contrast, which will just show the mucosal pattern, because complete filling can easily obscure the defects, as is shown in our cases. Serial films should therefore be taken, possibly without compression at the commencement of the examination, and after relaxation of the compression. It may be necessary to repeat the examination if there be any doubt as to the result. The diagnosis becomes more difficult if the cysts occur sporadically.

HINMAN refers to a dilatation of the terminations of the major calyces with constriction of the calicopelvic junctures and cystic dilatation at

the ureteropelvic junction with ureteral narrowing immediately below. He considers these signs typical of pyelitis cystica. They cannot be demonstrated in our case (II) in which some dilatation of the calyces and pelvis only is present, but in both our cases there is a narrowing of the ureteropelvic junction and a fusiform dilatation just below it where the defects are most prominent. These signs may be of diagnostic aid, but probably no accurate diagnosis can be made without the demonstration of typical vacuoles.

Cysts are often found in the bladder, especially at the base, by cystoscopy. The findings may suggest cysts in the upper urinary tract.

Differential Diagnosis

In one of our cases (I) the roentgen diagnosis of polyposis of the ureter was made; the clinical examination suggested the presence of a growth probably malignant. The roentgen appearance in this case was however characteristic of ureteritis cystica, if it only had been considered. Benign papillomas, which may be multiple, and malignant tumours are rare and most frequently located in the lower third of the ureter (PATCH et al.). The multiplicity and location together with the regular outline of the vacuoles in ureteritis cystica show roentgen appearance somewhat different from those conditions. Disseminated papillomas are seldom bilateral (CHEVASSU et al.). If the cysts cause occlusion of the ureter the resulting hydronephrosis may not be differentiated from that caused by other conditions.

Tuberculous granulations in the renal pelvis may show a similar picture as in one of our cases (II); clinical and laboratory investigations however may prove decisive. Mucosal relief films with a small amount of contrast may also be helpful, but on the whole, the diagnosis may be difficult to establish if the cysts are situated only in the pelvis alone and no typical vacuoles are visualized. Granulations of other origin should also be considered (ureteritis granulosa). Air bubbles (introduced during retrograde urography), blood clots, non-opaque concretions and stones, and the extremely rare haemangiomas should also be kept in mind.

Treatment

The treatment is primarily that of a chronic urinary infection and its complications (stones etc.). KINDALL has introduced the method of ureteral dilatation with tied-in catheters (2 to 3 days), with a view to mechanical rupture of the cysts, together with the instillation of a 1—2 per cent silver nitrate solution. Good results are reported, and the method seems to have been beneficial in one of our cases. KINDALL, KOPP have

Fig. 1. Case I. Rounded filling defects in the upper part of the right ureter. Narrowing at the uretero-pelvic junction. A filling defect in the upper part of the pelvis with regular outlines (mucosal fold?). Vacuoles in the left ureter at the level of L4 and its lower part.

demonstrated subsequent improvement by pyelography, as in one of our cases. The cysts may also rupture spontaneously. Uretero-nephrectomy may occasionally be indicated by reason of damage to the kidney. Conservative treatment may, however, often suffice and unnecessary surgical procedures should be avoided, because of the eventual bilateral nature of the condition. In our case in which nephrectomy was performed, as in some others in the literature, this might have been avoided if the correct diagnosis had been made.

Case Reports

Case I. G. A., female, aged 57. First attack of haematuria 18 years ago. Since then intermittent haemorrhage, usually lasting several days, more frequent during the past 10 years. 2 months prior to admission to hospital bleeding for about 4 weeks. Complains of tiredness, weakness and occasional pain in the loin.

Laboratory findings: Many leucocytes and bacilli in the urine but no red cells. Hb. 47 per cent. Red cells 2.1 millions. Index 0.85. White cells 4,240. Blood sedimentation rate 30 mm after 1 hour. Differential white count normal. B. P. 140/80. B. U. N. 14.8 mg per cent.

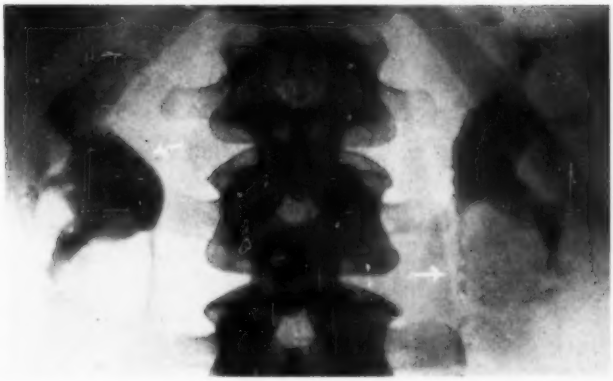


Fig. 2. Case II. Rounded vacuoles in left pelvis and calyces. Outlines uneven. Several vacuoles in right pelvis.

Oct. 1944 intravenous pyelography (State Hosp., O. P). Normal renal function. R. side: Kidney 11.5 × 6 cm of normal shape. Well-defined rounded filling defects, 1—2 mm in diameter, occupying the first 5 cm of the ureter down to the lower border of L3. There is a narrowing of the uretero-pelvic junction and immediately below this a moderate fusiform dilatation with compact nodular defects lying in clusters is seen. Rounded and regular defects are also present in the line of the ureter. The nodules are best visualized by a small amount of the contrast-medium. Pelvis and calyces normal. L. side: Kidney 13 × 6 cm, of normal outline. A kink is noted in the upper part of the ureter with moderate dilatation of the ureter and pelvis above its site.

Roentgen diagnosis: Polyposis of right ureter.

Ten weeks later an intravenous pyelogram reveals no change on the right side from previous examination. In the middle and lower part of the left ureter small filling defects are seen, and by a reexamination of the former films vague defects can be detected in them in the same situations.

In July 1949 the patient was admitted to hospital (St. Joseph's Hosp.) and in September as a tumor of the ureter was suspected right nephrectomy and partial uereterectomy (H. Hansen) was performed. The kidney proved to be normal, but about 5 cm of the uppermost part of the ureter were moderately dilated and thickened with numerous cysts of varying size covering most of the mucous membrane. Histological diagnosis: Ureteritis cystica (Univ. Patholog. Dpt., N. Dungal).

Case II. J. B., female, aged 48. Slight occasional dysuria now and then, without temperature, from the age of twenty. First attack of haematuria 7 years ago. Since then blood frequently in urine. Often complains of weakness, lassitude, headache and pains in the back. May 1947 massive haematuria and admitted to hospital for one month. Bleeding gradually subsided in a week. Intravenous urogram showed defects and ragged appearance of the left renal pelvis with small defects in the right. No bacteriological evidence of tuberculosis.

Sept. 1949 intravenous pyelography (State Hosp., O. P.) revealed normal renal excretion. Left side: Kidney 13 × 6 cm of normal outline. There are small round vacuoles and larger irregular defects in the pelvis and upper calyces outlines of which are uneven

Fig. 3. Case II. Complete contrast filling of left pelvis over-shadowing the defects. They are well seen in the upper part of the ureter, where the contrast-filling is moderate.

Fig. 4. Case II. After ureteral dilatation. No defects seen in the left ureter. Renal pelvis of same appearance as before treatment.

and ragged. Rounded or slightly oval well-defined defects, 2—5 mm in diameter, are seen in the ureter, most marked 2 cm below the uretero-pelvic junction where the uterer is a little dilated. Moderate dilatation of pelvis and calyces. Right side: Kidney 13 × 6 cm of normal shape. Pelvis and calyces dilated and ureter kinked. A few small defects in the pelvis, disappearing on more complete contrast-filling.

Roentgen diagnosis: Pyelo-ureteritis cystica.

A great number of red and white cells were present in the urine at that time. No bacteriological evidence of tuberculosis. Cystoscopy negative. Left ureteric catheterisation and dilatation with tied-in catheters no. 5 and 7 for 60 hours. Instillation of a 1 per cent silver nitrate solution (E. STEINTHÓRSSON).

The patient was re-examined in June 1950. She had no symptoms and the urine was normal. Intravenous pyelography revealed no changes in the ureters. The appearance of the renal pelves unchanged from previously. There was slight haematuria the day following the pyelography.

SUMMARY

Two cases of pyelo-ureteritis cystica are reported. One was diagnosed macroscopically and histologically, following operation, in the other the diagnosis was established by excretory pyelography. The radiological features of the disease are discussed and the etiology and pathogenesis briefly mentioned. The importance of a clinical diagnosis, if possible, before eventual surgical intervention, is pointed out.

ZUSAMMENFASSUNG

Es wird über zwei Fälle von Pyelo-ureteritis cystica berichtet. In einem Falle wurde die Diagnose im Anschluss an die Operation makroskopisch und histologisch gestellt, im andern ergab sich die Diagnose durch die Ausscheidungs-Pyelographie. Die radiologischen Merkmale der Krankheit werden besprochen und die Ätiologie und die Pathogenese kurz erwähnt. Es wird auf die Wichtigkeit einer klinischen Diagnose, möglichst vor einem etwaigen chirurgischen Eingriff hingewiesen.

RÉSUMÉ

Deux cas de pyélo-urétérite cystique sont relatés. L'un avait été diagnostiqué macroscopiquement et histologiquement à la suite d'une intervention chirurgicale, l'autre par la pyélographie excrétoire. Les données radiologiques de la maladie sont discutées, et l'étiologie et la pathologie brièvement mentionnées. L'importance du diagnostic clinique, précédant une intervention chirurgicale éventuelle, est rappelée.

REFERENCES

Arduino, L. J.: A case of pyelitis and cystitis cystica. J. Urol. 55 (1946), 149.

Bieberbach, W. D., Cook, P. H., and Goodale, R. H.: Pyeloureteritis cystica. With report of a case. Am. J. Roentgenol. 31 (1934), 778.

Bothe, A. E., and Cristol, D. S.: Cystic disease of the upper urinary tract. Pyelitis cystica and ureteritis cystica. Am. J. Roentgenol. 48 (1942), 48.

Burkland, C. E., and Leadbetter, W. F.: Pyelitis cystica associated with Hemophilus Influenzae infection in urine. J. Urol. 42 (1939), 14.

Cantrell, R. H., and Van Duzen, R. E.: Ureteritis cystica. Urol. & Cutan. Rev. 44 (1940), 641.

Chevassu, M.: Kystes épithéliaux disséminés sur la muqueuse du bassinet et de l'uretère des deux côtés. Diagnostic par l'urétéropyélographie rétrograde. J. d'urol. 41 (1936), 483.

Fagerström, D. P.: Proliferative tumors of ureter and renal pelvis, with further observations on significance of »epithelial cell nests»; 6 case reports. J. Urol. 59 (1948), 333. Ref. Yearbook of Urol. 1948.

Fite, E. H.: Report of a case of ureteritis cystica with result of treatment. Urol. & Cutan. Rev. 39 (1935), 91.

Gilbert, J. B.: Primary cancer of the ureter associated with ureteritis cystica. Case report. Urol. & Cutan. Rev. 40 (1936), 191.

Henke, F. and Lubarsch, O.: Handb. d. spez. Pathol. u. Histol. 1934.

Hinman, F., Johnson, C. M., and McCorkle, J. H.: Pyelitis and ureteritis cystica; three case reports with clinical diagnosis. J. Urol. 35 (1936), 174.

Jacoby, M.: Hypernephroider Krebs der Niere kombiniert mit Nierenbeckenstein, papillärer Krebs des Nierenbeckens und Harnleiters. Ztschr. f. Urol. 23 (1929), 718. — Ref.

Joelson, J. J.: Pyelitis, ureteritis and cystitis cystica; report of case showing urographic evidence of lesion in ureters and pelves. Arch. Surg. 18 (1929), 1570. — Ref.

Kindall, L. P.: Pyelitis cystica and ureteritis cystica; report of a case diagnosed by urography and confirmed by biopsy, with outline of treatment. J. Urol. 29 (1933), 645.

Knutsson, F.: The roentgen appearance in ureteritis cystica. Acta radiol. 16 (1935), 43.

Kopp, J. H.: Pyelitis, ureteritis and cystitis cystica. J. Urol. 56 (1946), 28.

Lowsley, O. S. and Kirvin, T. J.: Clinical Urology, Ed. II Baltimore. Vol. II 1944.

Morse, H. D.: The etiology and pathology of pyelitis cystica, ureteritis cystica, and cystitis cystica. Am. J. Path. 4 (1928), 33.

Orning, J.: Et tilfelle av pyelo-uretero-cystitis cystica. Nord. med. (Norsk mag. f. lægevidensk.) 9 (1941), 283.

Patch, F. S.: Pyelitis, ureteritis and cystitis cystica. New England J. Med. 220 (1939), 220.

— Primary tumors of the ureter. Urol. & Cutan Rev. 42 (1938), 625.

Pedroso, G. and Pedroso, R.: Pielo-ureteritis quística. Vida nueva 47 (1941), 207. — Ref.

Pessin, S. B.: Multiple cysts of ureters (ureteritis cystica); 7 cases; 2 associated with congenital polycystic kidneys. Urol. & Cutan. Rev. 43 (1939), 752.

Shumaker, E. J.: Cystitis, ureteritis and pyelitis cystica. Harper Hosp. Bull. 1 (1941), 42. — Ref.

Sterling, W. C.: J. A. M. A. 112 (1939), 1326.

— Extensive bilateral pyelo-uretero-cystitis cystica and glandularis producing pyonephrosis-nephrectomy; report of cases. J. Urol. 48 (1942), 237.

Toulson, W. H.: Ureteritis cystica with hematuria. Trans. Amer. A. Genito-Urin. Surg. 35 (1942), 191.

Wilson, G. H.: On epithelial cysts of renal pelvis, ureter and bladder. J. Path. & Bact. 39 (1934), 171.

Österbye, K.: To tilfælde af sjældne Uretersygdomme. Nord. med. (Hospitalstid.). 25 (1945), 197.

FROM THE RADIOLOGICAL CLINIC (DIRECTOR: PROFESSOR CARL KREBS),
UNIVERSITY OF AARHUS, DENMARK.

HODGKIN'S DISEASE OF THE OESOPHAGUS[1,2]

by

Jørgen Bichel.

The gastro-intestinal tract is frequently involved in generalized Hodgkin's disease (H. d.). The literature contains reports of more than 100 such cases. Even primary isolated malignant granuloma of the stomach has occasionally been observed. Involvement of the oesophagus seems to be rare. A search of the literature reveals that only about 15 cases have been reported up to the present time. Since mediastinal H. d. with invasion of the lung and dorsal spine is very common, it is, as pointed out by Weyde, remarkable that invasion of the oesophagus is not found more frequently. H. d. of the trachea with ulceration and invasion of the oesophageal wall, resulting in an oesophago-tracheal fistula has been described (PESONEN, FRIMANN-DAHL, HASLINGER). Simultaneous invasion of the trachea and oesophagus by a lymphogranulomatous mediastinal node has been observed in a few instances. Pulmonary abscesses may be the result (VIETA and CRAVER, KOTTLER). However, ulcerations need not occur. The lymphogranulomatous infiltrations may develop into polypoid, irregular tumour formations causing stenosis and secondary dilatation of the oesophagus (WEYDE, CHIOLERO, JACKSON and PARKER, WILLIAMS). By ordinary oesophagoscopic and radioscopic examinations the lesion will in such cases be indistinguishable from a cancer. Only a biopsy will give the diagnosis.

The lesions may probably originate in the oesophageal wall, but it is dubious whether a case of primary isolated H. d. of the oesophagus has ever been verified.

Even though it is rare, H. d. of the oesophagus is of some practical importance.

[1] The research on malignant disorders of the blood is supported by grants from Anders Hasselbalch's Fund, C. P. Schepler and Wife's Bequest, the Irma Foundation, and Lady Tata Memorial Foundation.

[2] Submitted for publication, Jan. 18, 1951.

If overlooked, the infiltrations in the oesophageal wall may cause the patient much trouble, and his condition may terminally become very miserable. However, according to the case reports, therapy can, in a remarkably large number of cases, bring complete relief from symptoms for several years.

As the benefit which the patient received from irradiation therapy in a recently observed case was very impressive, this case will be reported in the following to stress the importance of being on the look-out for oesophageal involvement in all patients with H. d. who complain of even the slightest dysphagia.

Case Report

(The Cancer Hospital 266/44.) A 21-year-old unmarried man was admitted to the Cancer Hospital. He complained of severe generalized itching of one year's duration, fatigue, and swelling of a lymph node in the right axilla. A biopsy specimen showed

Fig. 1. Oesophagus, May 1945 (right) and Sept. 1949 (left).

typical Hodgkin's granuloma. Irradiation was given to the swollen nodes, following which the patient was asymptomatic for about twelve months. However, in May 1945 he again complained of itching and now also of dysphagia. Roentgen films of the lungs were normal, but a roentgenogram of the oesophagus revealed irregularities and marked narrowing of the lumen at the level of the 4th dorsal vertebra (Fig. 1). Oesophagoscopy revealed a bulky irregular tumour in the anterior wall of the oesophagus 28 cm from the

teeth. The tumourous infiltrations extended 6—8 cm distally. The oesophageal wall corresponding to the infiltrated area was completely rigid. A biopsy specimen taken through the oesophagoscope showed a typical Hodgkin's granuloma. Roentgen rotation therapy was instituted, and a total of 4,400 r was administered to the affected area of the oesophagus (approx. 3,000 r in the tumour). In September 1945 a roentgenogram of the oesophagus showed normal conditions. The dysphagia had completely disappeared. During the following years enlarged nodes appeared in different regions, and the patient was treated at intervals with irradiation and nitrogen mustards, generally with good effect. Bone lesions in the lumbar column developed in 1947—48, but good symptomatic effect was obtained by roentgen treatment. During 1948—49 the patient was only partially incapacitated; yet he had to be treated with irradiation to nodes in the submental region. He often complained of severe generalized itching and received several series of nitrogen mustard, each of which was followed by a comparatively symptom-free period. During the winter of 1949 dyspeptic symptoms developed. Roentgenograms of the oesophagus were still normal, but large irregular bulky tumours were found in the stomach. His general condition now declined rapidly. Roentgen treatment and nitrogen mustards gave him but little relief, and he died in July 1950, extremely emaciated.

Autopsy showed enlarged mediastinal and peritoneal nodes and huge irregular tumours in the stomach extending from just below the cardia down over the greater curvature. However, in the oesophageal wall, which was entirely free of the enlarged mediastinal nodes, nothing abnormal was found. Histological examination of various nodes and the tumour in the stomach revealed a typical Hodgkin's granuloma.

SUMMARY

A case of Hodgkin's disease involving the oesophageal wall is presented. Even though it is rare, this localization has some practical importance, as irradiation treatment has in several cases rendered the patients symptom-free for long periods.

ZUSAMMENFASSUNG

Ein Fall von Hodgkin'scher Krankheit, bei dem die Oesophagus-Wand ergriffen war, wird mitgeteilt. Dieser Lokalisation kommt trotz ihrer Seltenheit eine gewisse praktische Bedeutung zu, da die Strahlenbehandlung die Patienten in mehreren Fällen für lange Perioden symptomfrei machte.

RÉSUMÉ

Un cas de maladie de Hodgkin intéressant la paroi oesophagienne est relaté. Malgré que cette localisation soit rare elle a une certaine importance pratique, car le traitement par irradiation a soulagé les malades dans plusieurs cas et les a même délivrés de symptômes pour de longues périodes.

LITERATURE

WEYDE, R.: Nord. med. 29 (1946), 20.
PESONEN, N.: Duodecim 54 (1938), 757. Ref. in Nord. med. 3 (1939), 2373.
FRIMANN-DAHL, J.: Norsk mag. f. lægevidensk. 97 (1936), 1273.
RATKOCZY, N.: Die Pathologie und Therapie der Lymphogranulomatose. G. Thieme, Leipzig 1940.

Sternberg, C.: Ergebn. d. allg. Path. u. path. Anat. 30 (1936), 1.
Lignac, G. O. E.: Krkhforsch. 9 (1932), 125.
Hedinger, E.: Schweiz. med. Wchnschr. 2 (1923), 828.
Chiolero, J.: Ann. d'anat. path. 12 (1935), 305.
Hirschfeld, H. and Isaac, A.: Med. Klin. 3 (1907), 1580.
Haslinger, F.: Arch. f. Ohren-, Nasen- u. Kehlkopfh. 150 (1941).
Jackson, H. and Parker, F.: Oxford University Press, New York (1947), 59.
Williams, R.: Brit. J. Radiol. 8 (1935), 265.
Vieta, J. O. and Craver, L. F.: Radiology 37 (1941), 138.
Kottler, R. I.: Ztschr. f. Tuberk. 58 (1930), 37.
Hayden, H. C. and Apfelbach, C. W.: Arch. Path. 4 (1927), 743.
Ennuyer, A. et al.: Paris méd. 40 (1950), 164.
Doumer, E. et al.: Arch. d. mal. de l'app. digestif 37 (1948), 775.
Askanazy: Rev. méd. de la Suisse Rom. 12 (1929), 775.
Scott and Forman: Ohio State M. J. 12 (1916), 323.

DEPARTMENT OF PHYSICS (DIRECTOR: F. BĚHOUNEK, D.SC.), STATE RADIOTHERAPEUTICAL INSTITUTE, PRAHA-BULOVKA, CZECHO-SLOVAKIA.

THE MESOTHORIUM-RADIUM BEAM UNIT[1]

by

F. Běhounek, D. Sc. and *J. Klumpar*, D. Sc.

Larger amounts of mesothorium are scarcely used in gamma-ray therapy because of the relatively short period (6.7 years) of $MsTh_2$. On the other hand they present, if suitably old, an advantage against the radium by the greater penetrance of their gamma rays, which is chiefly due to the intense spectral line of ThC″ having an energy of 2.62 MeV. This difference between the penetrating power of gamma rays from Ra and MsTh must result in the slower decrease of the depth dose of MsTh as compared with that of Ra and consequently in a better irradiation of deeply situated tumours. This reason lead us to work out a mesothorium beam unit when in autumn 1945 concentrated mesothorium salts of more than 3 grams of radium gamma equivalent became available.

Unfortunately we received the mesothorium salt already filled in the tubes as sulphate which rendered the determination of respective amounts of the three elements, MsTh, RdTh and Ra, much more difficult. Although such an analysis is not of prime importance for therapeutical purposes, it is nevertheless a valuable guide as much as the dependence of the gamma rays intensity of the unit on the age of the mesothorium source is concerned.

The intensity of gamma rays from MsTh and its decay products as measured by the ionization effect is a complicated function of time. Assuming that for the time $t = 0$ no RdTh was present and that the ionization effect of RdTh and its products exceeds this effect of MsTh (1 + 2) by a factor of 1.5 we obtain for the time dependence of the intensity J of gamma rays from MsTh + RdTh salts a curve plotted in Fig. 1.

[1] Submitted for publication, Dec. 1, 1950.

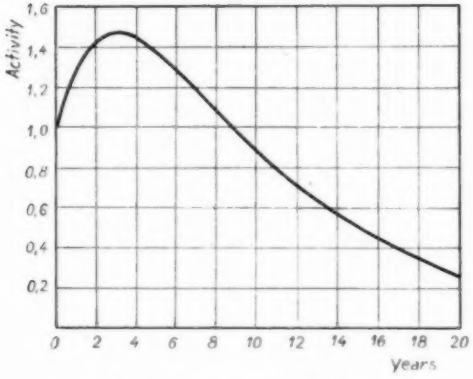


Fig. 1. Time curve of MsTh-activity measured by gamma rays.

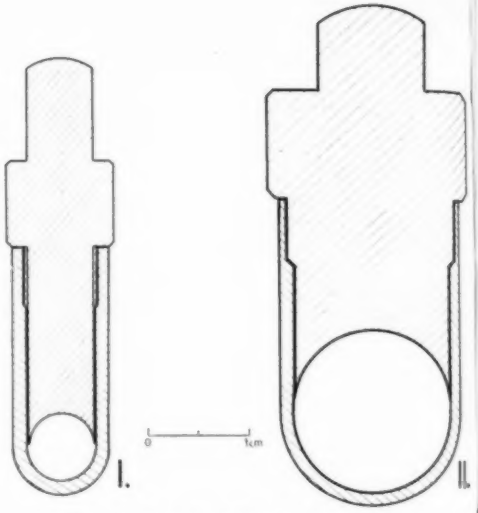


Fig. 2. Tubes of stainless steel for mesothorium salts.

As we knew nothing about the origin of our MsTh salts and as furthermore we received them already in the form of insoluble sulphates filled and sealed in tubes, it was impossible to determine, by the emanation method, their content of individual constituents, *i. e.* of MsTh, RdTh and even of Ra always present in mesothorium salts in consequence of its isotopy with $MsTh_1$. Nevertheless an attempt has been made to check at least *the radium gamma equivalent* (= R.G.E.) of MsTh and RdTh using the absorption method first indicated by HAHN (1) and developed afterwards by BOTHE (2) and SIEVERT and OLSSON (3) although the precision of the method is none too adequate.

The total amount of the MsTh salt, as we received it, equalled in September 1945 3,050 mg of R.G.E. when filtered with 0.5 cm of lead (basic filtration of HAHN and BOTHE) and was divided into 16 tubes (Fig. 2), 15 of them smaller and of identical size (= type I) and 1 larger (type II). All tubes are of stainless steel and the rays are filtered by 1 mm Fe in the main direction of the beam. The radioactive salt forms a sphere having the diameter of 5 mm in the smaller tubes and 12 mm in the larger one. The weight of this salt is very constant, equalling in every small tube (0.1566 ± 0.0006) grams; the average of the R.G.E. of the small tube is 182.3 mg of the Ra with the range from 179 to 184 mg. The large tube contains 0.8975 grams of salt with 333 mg of R.G.E.

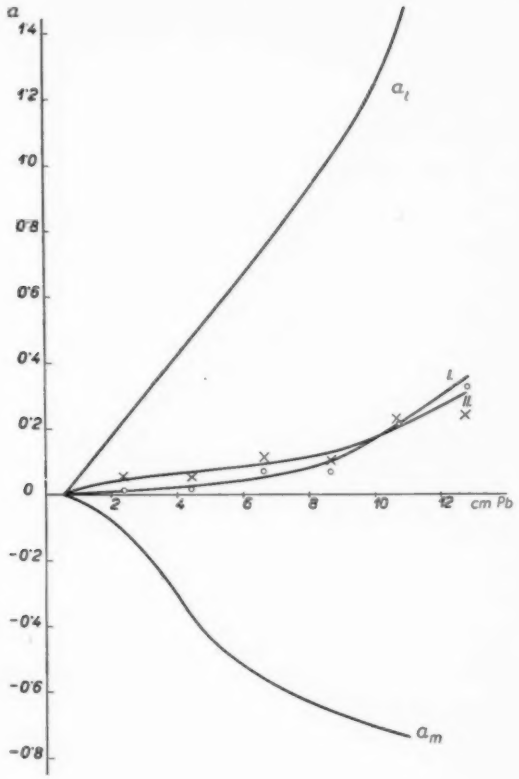


Fig. 3. Radium gamma equivalents (a) diminished by 1 as function of filter thickness for 0.5 cm Pb of basic filtration. a_m for pure MsTh, a_l for pure RdTh, *I*, *II*, experimental values for small tubes (*I*) and the large one (*II*).

As the tubes were not air-tight at the moment where we received them for the first time, it was possible to control the qualitative composition of their salts by the emanation method. The presence of the thorium emanation (thoron) was tested by the measurement of its induced activity: surprising was the discovery that whilst the radon was very readily given off, the thoron escaped from the tubes only when a marked difference in pressure existed between the air in the tubes and the air surrounding them (4).

The determination of the R.G.E. of MsTh and RdTh by the absorption method is based upon the differences of the average penetration of the gamma rays emitted by Ra, MsTh and RdTh. According to RUSSELL (5) the mean linear absorption coefficient in the lead equals 0.50 cm^{-1} for Ra, 0.62 cm^{-1} for MsTh and 0.46 cm^{-1} for RdTh. The consequence of this absorption inequality is that the R.G.E. of MsTh

Fig. 4. Apparatus for the measurement of radium gamma equivalents. (*A* ionization chamber, *B* central cavity of the chamber, *S* gamma ray source, *T* tube shielding connection from the chamber to electrometer, *E* Wulf electrometer, *C* auxiliary condenser, *F* cylindrical lead filters.)

and RdTh becomes a function of the filter thickness d. This function decreases with increasing d for MsTh and increases with d for RdTh. BOTHE followed this dependence of R.G.E. on d up to the total thickness of 11 cm of lead separately for each of the pure elements of MsTh and RdTh and then plotted the respective R.G.E. values against the d values. In this way he obtained 2 curves, a_m, a_t (Fig. 3) which he used afterwards for the determination of the R.G.E. of individual elements, Ra, MsTh and RdTh, present in the mixed salts.

To find out the fractional R.G.E. of the constituents it is sufficient to effectuate only two measurements (besides the basic measurement with 0.5 cm lead filtration according to BOTHE) with filters of various thicknesses. For the R.G.E. of the three elements following relations can be deduced:

$$m = \frac{a_1 a_{t_2} - a_2 a_{t_1}}{a_{m_1} a_{t_2} - a_{m_2} a_{t_1}} \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

$$t = \frac{a_2 a_{m_1} - a_1 a_{m_2}}{a_{m_1} a_{t_2} - a_{m_2} a_{t_1}} \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (2)$$

$$m + t + r = 1 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (3)$$

Now m, t and r are the respective fractional values for R.G.E. of MsTh, RdTh and Ra and a_1, a_2 are the measured R.G.E. for the filter thickness d_1 and d_2 compared to the basic R.G.E. ($d = 0.5$ cm Pb) and diminished by 1. Further coefficients, a_{m_1}, a_{m_2}, a_{t_1} and a_{t_2}, are deduced in the same way as the coefficients a_1 and a_2 from the curves a_m and a_t plotted by BOTHE for pure MsTh and RdTh (Fig. 3).

To examine the intensity of gamma rays of our tubes with various filters we used a cylindrical closed ionization chamber with the central cavity, where the radiant sources, surrounded with Pb-filters, were placed. The outer diameter of the ionization chamber was 68 cm and its height 15 cm, while the diameter of the central cavity was 33 cm. The cylindrical inner electrode of the chamber, well isolated with amber, was connected by a 150 cm long perfectly shielded wire with a bifilar Wulf electrometer (Fig. 4). In order to reduce the rate of the electrometric discharge for small values of the filter thickness an auxiliary plate condenser could be attached to the electrometer. The condenser had a capacity of 568 cm and reduced the rate of discharge in relation of 4.89 : 1. As radium standard three tubes containing the total of 51.9 mg of Ra-element were employed and their filtration of 1 mm iridio-platinum taken in account. The maximum lead filtration used amounted to 12.85 cm.

Table 1

cm *Pb*	a_m	a_t	a_I	a_{II}
11.....	−0.74	+1.475	+0.225	+0.215
10.....	−0.70	1.225	0.165	0.175
9.....	−0.66	1.05	0.110	0.145
8.....	−0.62	0.92	0.080	0.120
7.....	−0.575	0.79	0.060	0.100
6.....	−0.525	0.655	0.045	0.085
5.....	−0.440	0.542	0.035	0.075
4.....	−0.305	0.42	0.025	0.055
3.....	−0.180	0.297	0.023	0.040
2.....	−0.078	0.175	0.020	0.025

The results of the measurements are shown as curves I and II in Fig. 3, where index I denotes small tubes and index II the larger one. The numerical values of various a-coefficients are summarized in the Table 1 and the resulting R.G.E. of MsTh, RdTh and Ra in the 1st section of Table 2. In both tables the indexes I and II have the same meaning as in the Fig. 3, denoting the values for small tubes or the large one respectively. The surprisingly high content of RdTh and Ra in the large

tube II is a result of its composition as a mixture of various low concentrated samples of MsTh-, RdTh- and Ra-salts.

Table 2

Method	m_I ($MsTh_1$)	t_I (RdTh)	r_I (Ra)	m_{II} ($MsTh_1$)	t_{II} (RdTh)	r_{II} (Ra)
1. BOTHE, basic filtr. 0.5 cm Pb	34 ± 4	31 ± 2	35 ± 5	5.5 ± 1	17 ± 1	77.5 ± 2
2. BOTHE, basic filtr. 3.0 cm Pb	20 ± 2	36 ± 2	44 ± 4	4 ± 3	22 ± 1	74 ± 4
3. SIEVERT-OLSSON, basic filtr. 3.0 cm Pb	40 ± 4	38 ± 3	22 ± 7	6 ± 3	22 ± 3	72 ± 6

As can be seen from Table 2 the accuracy of the results is not altogether satisfactory although the mean values were computed by the square root method from 28 different paired-values of Pb thicknesses.[1]

When comparing the BOTHE's procedure with that of SIEVERT and OLSSON we see first that these authors relate their measurements of gamma ray intensity to the basic R.G.E. for 3.0 cm Pb instead of 0.5 cm Pb as BOTHE did and furthermore that their a_m-curve differs notably from that of BOTHE, as can be seen from Fig. 5.

Table 3

cm *Pb*	$_sa_m$	$_ba_m$	a_t	a_I	a_{II}
11	−0.46	−0.64	+0.87	+0.196	+0.168
10	−0.42	−0.615	0.725	0.136	0.129
9	−0.38	−0.585	0.60	0.085	0.109
8	−0.33	−0.55	0.487	0.056	0.078
7	−0.285	−0.50	0.38	0.036	0.058
6	−0.232	−0.42	0.28	0.021	0.043
5	−0.175	−0.30	0.18	0.011	0.034
4	−0.10	−0.15	0.087	0.002	0.014
3	−0.00	−0.00	0.00	0.000	0.000

$_sa_m$ = SIEVERT and OLSSON's values for MsTh. $_ba_m$ = BOTHE's values for MsTh. a_I, a_{II} = radium gamma equivalents − 1 for MsTh-tubes.

[1] In combining the results of measurements into pairs according to various d-values, it has been found that certain combinations are precluded (*e. g.* 9 cm and 3 cm, 7 cm and 4 cm, 6 cm and 5 cm of Pb) because of leading to the zero value of denominator in relations (1) and (2). It is clear that even combinations taken from the vicinity of these which are critical must be omitted since the denominator acquires a too small value and the final result is subject to great errors.

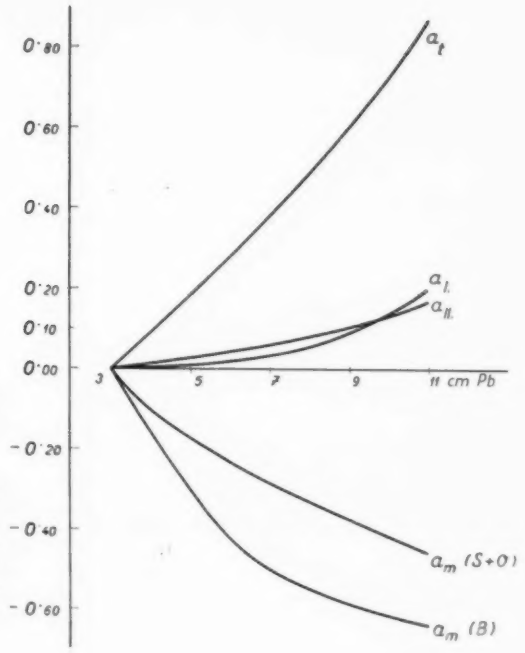


Fig. 5. Radium gamma equivalents (a) as function of filter thickness for 3.0 cm Pb of basic filtration.
a_t for RdTh (BOTHE, SIEVERT and OLSSON), a_m $(S + O)$ for MsTh according to SIEVERT and OLSSON, a_m (B) for MsTh according to BOTHE, a_I, a_{II} experimental values for small tubes (I) and the large one (II).

In view of these differences we proceeded on further computation taking first BOTHE's curves as a base but in combination with the basic R.G.E. for 3 cm Pb and then with SIEVERT-OLSSON's curves and 3 cm Pb as basic R.G.E. (Table 3.) The results obtained by these two procedures and inserted in the 2nd and 3rd section of Table 2 differ notably from those of the 1st section as far as the 15 small tubes are concerned, while the difference for the Ra gamma ray intensity of the central tube is relatively unimportant.

It is likely that the values obtained with SIEVERT-OLSSONs data are nearer to the actual facts for following reasons:

1. The HAHN's values for a_m agree with those of SIEVERT and OLSSON (cf. reference /3/).
2. BOTHE himself considers his a_m-curve as provisory.
3. The most current content of Ra in concentrated and not too old MsTh salts ranges from 20 to 30 % (cf. refer. /5/, p. 299) which agrees with the result obtained from SIEVERT-OLSSON's curves.

We, therefore, take as the most probable values of R. G. E. (40 ± 4) % for MsTh, (38 ± 3) % for RdTh and (22 ± 7) % for Ra as far as the

small tubes are concerned and (6 ± 3) % for MsTh, (22 ± 2.5) % for RdTh and (72 ± 6) % for Ra in the case of the large tube.

In resuming our measurements of R.G.E. of various elements which can be present in MsTh-salts and the analysis of the results we find that the main reason of the poor accuracy of absorption method is due to the fact that the method is an indirect one using the difference of two quantities. By these substractions the experimental errors, in themselves not considerable, are many times multiplied, thus affecting the final result in the same degree. Notwithstanding these defects, the absorption method represents to-day the unique means enabling us to obtain some information about the radium gamma equivalent (R.G.E.) of various radioisotopes present in concentrated mesothorium salts which are sealed and inaccessible to another method of investigation.

2. *The beam unit.* As usually the SIEVERT's pattern (6) of the beam unit affording the best protection of the personnel has been chosen but its achievement has been somewhat simplified as shown in Figs. 6 and 7. The holder of the tubes with MsTh-salts is transferred electro-mechanically from the safe inlaid with 10 cm of Pb and fixed to the ceiling of the treating room. It passes through a vertical brass tube which is rigid and can be turned round its axis, into a flexible steel pipe provided with a brass nozzle which is the site of the holder when in radiant position. The setting up of patients for treatment is performed with the holder in the safe, while every other operation (*i. e.* the opening of the safe and the transfer of the holder from safe to nozzle and vice-versa) proceeds by remote control from the table placed outside the treating room. The motion of the holder can be watched through a window in the door by means of a movable index (Fig. 7). Notwithstanding this arrangement and the light signals marking exactly every step of the operation on the control board, it happened sometimes by the negligence of the personnel that the shutter of the safe was closed while the holder was still in radiant position or half-way to the safe and in consequence injured the traction cable. This was the most serious defect encountered during the three years of use of the unit. To do away with this deficiency a blocking arrangement was provided in the design of another unit preventing closing of the safe as long as the holder is still outside.

3. *Protection of the personnel.* When applying the bomb to the patient, the doctor and his assistant are protected by a minimum of 10 cm Pb (or its equivalent) and by a minimum distance of about 70 cm, this length being taken from the source inside the safe to the top of the head of a person 180 cm tall. Thus the intensity of the whole of 3,050 gms of R.G.E. is reduced by screenage to 1/130 and by distance to a further fraction of 1/4,900, totalling to $1/6.37 \times 10^5$. The resulting dose-rate in

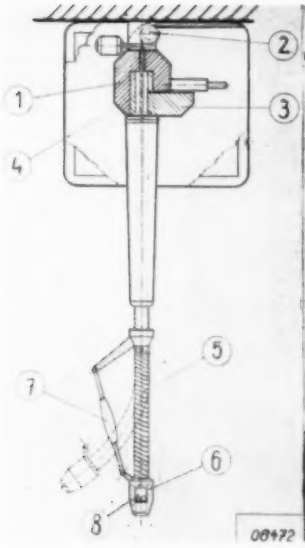


Fig. 6. Fig. 7.

Fig. 6. Scheme of the mesothorium beam unit.
(1) steel safe inlaid with 10 cm of Pb, (2) electro-mechanical transferring system, (3) safe shutter operated mechanically by remote control, (4) steel cable, (5) flexible steel tube, (6) nozzle with 2 cm Pb-mantle, (7) screw controlling the flexion of the pipe and raising the nozzle, (8) holder with MsTh-tubes.

Fig. 7. View of the mesothorium beam unit.
S safe, C_1 connection to the shutter, C_2 connection to the holder of MsTh-tubes, *J* moving index showing the position of the holder, *R* rigid rotating tube, *F* flexible steel tube, *N* nozzle containing the holder in radiant position, *P* lever device controlling *F*.

the point under consideration amounts then to 0.0382 *r*/hour. Since the setting up of patients for treatment requires at most 3 minutes and every treatment 1 hour, the doctor and his assistant receive by this work at most a dose of 0.0115 *r* during a working day of six hours a day. With regard to the fact that only the top of the workers' heads is exposed to this dose, the protection can be considered perfect.

There are somewhat worse conditions for the personnel manipulating the unit and watching the patient through the door-window, the only worth while protective means in this case being the distance of about 450 cm. This distance reduces by the square law the radiation of the source to a dose-rate of 0.121 *r*/hour. When the average time taken for

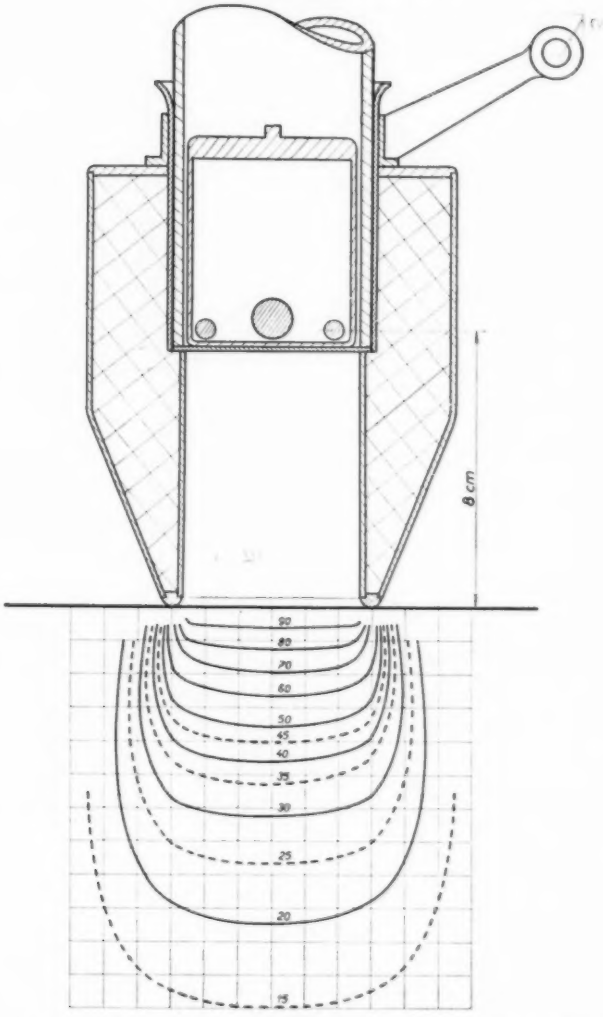


Fig. 8. Radiation field of mesothorium beam unit. (Depth doses in percentage of the skin dose.)

one complete remote operation of the unit (*i. e.* opening of the safe, transfer of the holder into radiant position and back to the safe and closing the safe) equals 1 minute and the observation of the patient during irradiation another minute (six times ten seconds), the worker

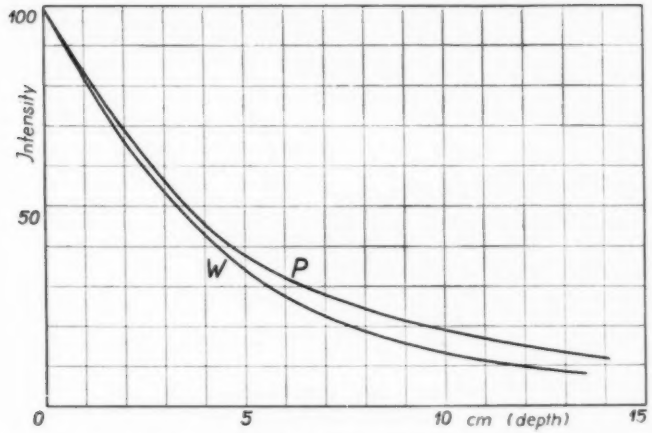


Fig. 9. Percentage decrease of intensity of the beam with the depth. *P* for mesothorium unit, *W* for Westminster 4-gram unit.

receives a total dose of 0.024 *r* during a working day of six hours. This is of course the maximum dose he can get with the beam directed towards the door of the treating room; however such a position of the nozzle is exceptional and in case of other directions of the beam the worker is protected by the lead mantle of the nozzle, reducing the dose to about 30 % of its maximum value given above. In any case the fact that the *whole body* of the worker receives the above dose is an unfavourable one.

4. *The depth doses.* Before a definite arrangement of the tubes in the holder has been designed preliminary measurements were effectuated with a model of the holder with tubes in different positions. The aim of this work was to achieve the best lateral distribution of the dose. As it could be foreseen from theoretical point of view the most satisfactory solution was that with the large tube (333 mg R.G.E.) in central position and with the 15 small tubes arranged periferally in equal distances (Fig. 8). Since the majority (about 90 %) of the radioactive matter forms a layer constituted by the spheres having 5 mm of diameter, the radiation plane is well defined and the measurements of depth doses can be theoretically checked.

The depth isodose curves as shown in Fig. 8 were determined radiographically by a new method elaborated by one of us (KLUMPAR), which will be published. By this method only 1 photographic film is used. It is placed between the plates of a wooden phantom in a position slightly inclined to the central axis of the beam. The absolute dose values in *r*-

units are based on the ionization measurements performed in the phantom along the central axis of the beam with the help of Victoreen dosemeter and SIEVERT condenser chambers. The respective curve showing the decrease of intensity of the beam with the depth is plotted under *P* in Fig. 9. For a comparison a corresponding curve has been derived from the radiation field of Westminster Hospital 4-grams unit filled with radium only (7) and embodied in Fig. 9 under *W*. The Westminster unit with small port presents similar irradiation conditions to our mesothorium unit as far as the FS-distance and the skin dose are concerned.[1] As can be seen from Fig. 9 the gradient of the depth dose is less for MsTh-unit than for Ra-unit. So *e. g.* the dose in 10 cm corresponds to 19 % of the skin dose for MsTh-unit and to 13 % only for Ra-unit, *i. e.* the depth dose in 10 cm is by 46 % higher for MsTh-unit than for Ra-unit as was expected.

SUMMARY

After an account and discussion of the analysis of mesothorium salts by the absorption of gamma rays, a description of a mesothorium beam unit with 3.05 gms of radium gamma equivalent is given and a better depth dose distribution of this unit in comparison to a radium one demonstrated.

ZUSAMMENFASSUNG

Nach einer Wiedergabe der Ergebnisse der Analyse von MsTh-präparaten nach der Methode der Absorption von Gammastrahlen und ihrer Bewertung, wird die Konstruktion einer MsTh-Bestrahlungseinheit, 3.05 g Gamma-aeq. enthaltend, beschrieben. Es wurde bei ihr eine bessere Verteilung der Tiefendosen als bei Radiumbestrahlungseinheiten gefunden.

RÉSUMÉ

Après avoir procédé à l'analyse des sels du mésothorium à l'aide de l'absorption des rayons gamma et à la discussion de cette méthode, on décrit un appareil de télécuriethérapie contenant le mésothorium dont le rayonnement gamma équivaut à 3.05 g de radium. On démontre que la répartition des doses en profondeur est plus favorable en cas de cet appareil qu'en cas de celui qui ne contient que le radium.

REFERENCES

(1) O. HAHN: Strahlentherapie *4* (1914), 154; Le Radium, *11* (1944), 71.
(2) W. BOTHE: Z. f. Phys. *24* (1924), 10.
(3) R. M. SIEVERT and E. OLSSON: Acta Radiol. *12* (1931), 121.
(4) F. BĚHOUNEK and J. KLUMPAR: Nature *160* (1947), 640.
(5) S. MEYER and E. SCHWEIDLER: Radioaktivität, Verlag Teubner, Berlin 1927.
(6) R. M. SIEVERT: Acta Radiol. *18* (1937), 157.
(7) H. T. FLINT and C. W. WILSON: Brit. J. Rad. *8* (1935), 426; *11* (1938), 112.

[1] The skin dose of Westminster unit with small port (aperture 3.5 cm) is 480 *r*/hour, while the skin dose of MsTh-unit computed for 4 gms of R.G.E. from the actual value of 6.1 *r*/min. amounts to 497 *r*/hour.

FROM THE ROENTGEN DEPARTMENT (DIRECTOR: PROFESSOR ERIK LINDGREN)
OF THE SERAFIMERLASARETTET, STOCKHOLM, SWEDEN.

RADIOGRAPHIC FINDINGS IN 14 CASES OF STURGE-WEBER SYNDROME[1, 2]

by

Giovanni Di Chiro and *Erik Lindgren.*

The question of the diagnosis of neurocutaneous angiomatous malformations has become much more accurate since WEBER (1922) (16), and DIMITRI (1923) (4), first described radiographically demonstrable intracranial calcification often of characteristic appearance. STURGE-WEBER syndrome may be confidently diagnosed when the typical radiographic appearances of certain intracranial calcifications are added to the cardinal clinical signs and symptoms (»port-wine» naevus, glaucoma and convulsive seizures).

In the present work the authors have carried out a systematic study of a comparatively large number of cases of STURGE-WEBER syndrome from the radiological viewpoint, and have attempted to find out whether radiology can give more information than the presence of typical calcification alone. Furthermore due consideration has been given to the possibility of obtaining information of assistance to the clinician in those cases where the intracranial calcification is atypical or not demonstrable.

The work is based upon 14 cases of which 10 were pathologically verified. The other cases are so typical that we have considered the diagnosis to be reliable. All the fourteen cases have been examined radiologically with preliminary films. Encephalography has been used in eleven cases, internal carotid angiography in seven, and external carotid angiography in one. The cases have been collected from the Roentgen Department of the Serafimer hospital and the clinical and pathological data taken from the clinical records of the hospital.

[1] We have preferred the term STURGE-WEBER syndrome to STURGE-WEBER-KRABBE, STURGE-WEBER-DIMITRI, STURGE-WEBER-KALISCHER or encephalotrigeminal angiomatosis, as one being in more common use.

[2] Submitted for publication, Jan. 10, 1951.

Case 14 has been reported already by BERGSTRAND, OLIVECRONA and TÖNNIS (1) (case 4 in the series of these authors).

Case Summaries

(Legend: P. A. D. = pathologically verified)

1. E. T. N. ♂ 13 yrs. Convulsive seizures since 9 yrs of age. Physically underdeveloped. Retarded mental development.

Rtg. Calcifications in both occipital lobes, typical and more marked on the right side, atypical on the left. *Encephalography:* normal.

2. U. L. Z. ♂ 10 yrs. Typical »port-wine» naevus involving the right forehead and adjacent upper eyelid. Very frequent convulsive seizures since 3 yrs of age. Slight paresis of left arm and leg. Arrested mental development.

Rtg. Asymmetrical skull: right side of the cranial vault underdeveloped. Extensive, typical calcification involving right occipital and temporal lobes. *Encephalography:* posterior part of right lateral ventricle larger than left. Strikingly enlarged subarachnoid spaces over right convexity. P. A. D.

3. O. P. P. ♂ 34 yrs. Convulsive seizures since 6 months of age. Headaches. Slight mental deterioration.

Rtg. Asymmetrical skull: underdevelopment of left cranial vault most marked posteriorly. Typical calcification involving left occipital lobe. *Encephalography:* left trigonum dilated. Some widening of subarachnoid spaces on the left side. P. A. D.

4. G. I. K. ♂ 2½ yrs. Typical »port-wine» naevus on left cheek and around left eye. Left-sided glaucoma. Jacksonian convulsive seizures since 5 months of age. Right hemiparesis.

Rtg. Skull strikingly asymmetrical: left side of the cranial vault underdeveloped. Typical calcification involving left occipital lobe. There is a large pacchionian granulation in the region of the calcification drained by a large venous channel. *Encephalography:* some widening of subarachnoid spaces on left. *Internal carotid angiography:* (left side) normal.

5. A. S. L. ♂ 28 yrs. Extensive, typical »port-wine» naevus involving supraorbital region, eyelids, and cheek on the left side as well as the nose. Convulsive seizures since 3 yrs of age. Weakness of right arm. Slight underdevelopment of extremities on the right side.

Rtg. Asymmetrical skull: left side of the cranial vault underdeveloped. Widened vascular channels in left parietal and frontal regions. Typical calcification in left parieto-occipital region. *Encephalography:* subarachnoid spaces strikingly enlarged over left convexity. *Internal carotid angiography:* (left side) many small vessels are filled by posterior cerebral artery.

6. L. C. ♂ 26 yrs. Typical »port-wine» naevus involving left side of the forehead and left eyelid. Convulsive seizures since 10 months of age. Right hemiparesis.

Rtg. Asymmetrical skull: vault underdeveloped on left side posteriorly. Widened vascular channels in left parietal region. Huge, typical calcification involving left parietal and occipital lobes. Present very large frontal air sinuses. *Encephalography:* considerable widening of subarachnoid spaces over left convexity.

7. E. H. J. ♂ 25 yrs. Severe migraine. Deterioration of vision.

Rtg. Typical calcification in right occipital lobe. *Internal carotid angiography:* (right side) normal. P. A. D.

8. Y. L. S. ♂ 16 yrs. Convulsive seizures since 7 yrs of age. Headaches. Deterioration of vision.

Rtg. Widened vascular channels in left parietal region. Atypical calcification in left occipital lobe. *Encephalography:* left lateral ventricle enlarged. *Internal carotid angiography:* (left side) normal. P. A. D.

9. V. M. A. ♂ 17 yrs. Convulsive seizures since 15 yrs old.

Rtg. Asymmetrical skull: right side of the cranial vault underdeveloped. Typical calcifications involving both occipital lobes but much more marked on right. P. A. D.

10. E. A. V. ♀ 16 yrs. Convulsive seizures since 8 months of age. Headaches. Slight retardation of mental development.

Rtg. Asymmetrical skull: vault underdeveloped over calcification. Typical calcification in right occipital lobe. *Encephalography:* left trigonum dilated. P. A. D.

11. U. C. T. ♀ 21 yrs. Atypical naevus, *i. e.* without »port-wine» staining, on right cheek. Convulsive seizures since 16 yrs of age. Right hemiparesis. Impairment of speech.

Rtg. Atypical calcification in left parietal lobe near mid-line. *Encephalography:* normal. *Internal carotid angiography:* (left side) normal. P. A. D.

12. U. B. J. ♀ 4 yrs. Jacksonian convulsive seizures. Anaemia. Haemorrhagic tendency.

Rtg. Asymmetrical skull: right side of cranial vault underdeveloped. Widened vascular channels in frontal region. *Encephalography:* right lateral ventricle enlarged. Some widening of subarachnoid spaces on right side. *Internal carotid angiography:* (right side) normal. P. A. D.

13. E. V. P. ♀ 14 yrs. Headache, vertigo, paresthesia of right hand for one year. No previous symptoms.

Rtg. Asymmetrical skull: left side of the cranial vault underdeveloped posteriorly. *Internal carotid angiography:* (left side) anterior cerebral artery displaced to the right. The branches of the middle cerebral artery are stretched around an avascular zone. P. A. D.

14. L. L. ♂ 35 yrs. Typical »port-wine» naevus involving left side of forehead, left eyelids, and left cheek. Leftsided glaucoma. Convulsive seizures since 3 yrs of age, but between 7 and 32 yrs of age free from symptoms.

Rtg. Asymmetrical skull: left side of the cranial vault underdeveloped. Widened vascular channels in left frontal and parietal regions. Atypical calcification in left occipital lobe. *Internal carotid angiography:* (both sides) enlarged veins frontally and parietally on left side. *External carotid angiography:* (both sides) left middle meningeal artery somewhat wide. P. A. D.

Discussion

Conventional radiograms

Skull asymmetry: In our series this sign is fairly frequent (10 cases). The underdeveloped part of the skull always corresponds to the cerebral lesion (Fig. 1 and 2). The asymmetry is often more marked posteriorly due to the more frequent posterior localization of the brain lesion. In most cases therefore the asymmetry is best shown in the half-axial view taken in the supine position (the tube is tilted 30—35 degrees cranially).

Fig. 1. Case 5. Typical calcification in the left parieto-occipital region. Note the considerable asymmetry (half-axial view).

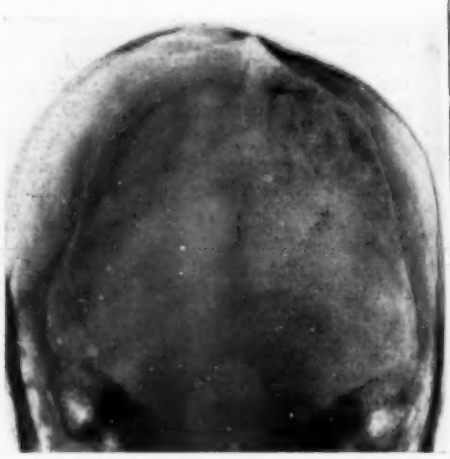
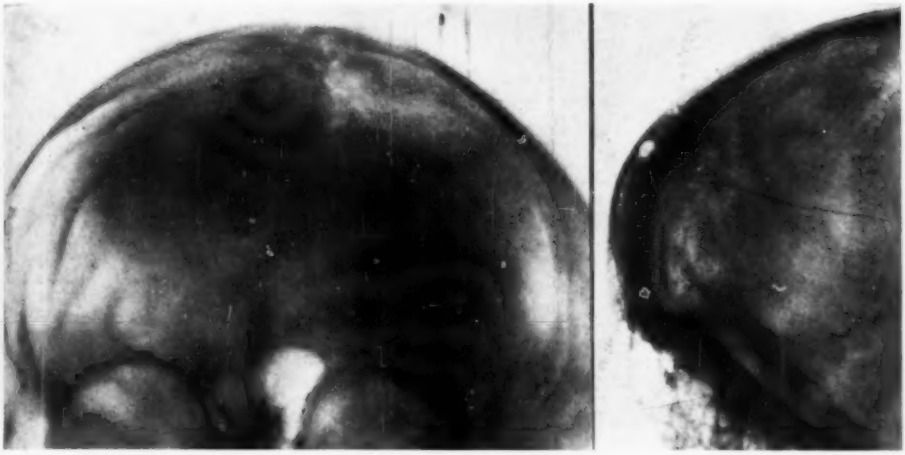


Fig. 2. Case 4. Marked asymmetry. The left side of the cranial vault is underdeveloped especially over the calcification.

This sign was noted in one case by GREEN, FOSTER and BERENS (7), was present in the radiograms but not commented on in the case of HEUBLEIN, PENDERGRASS and WIDMANN (8), and was reported only as clinical sign in the one case of MONIZ and LIMA (13). In our opinion it merits more attention. The asymmetry is sometimes so striking that it can be seen on clinical inspection: nevertheless more often than not it can be shown only by roentgenography. The importance of the sign lies not only in its frequence but also in certain theoretical considerations. We are as yet uncertain today whether the cerebral component of STURGE-WEBER syndrome can be considered as a developmental abnormality, or as a lesion secondary to pial angiomatosis on the basis of nutritional disturbances. The asymmetry of the skull as well as the nearly constant microgyria points to early brain damage.[1] There are authors in fact who consider the STURGE-WEBER syndrome a general developmental error similar to the tuberose sclerosis of BOURNEVILLE (KRABBE (9)).

Enlarged vascular channels of the skull: Noted once by BROCK and DYKE (2), present in the one case of MONIZ and LIMA (13), and found once in the 5 cases of BERGSTRAND, OLIVECRONA and TÖNNIS (1). These changes are present in six cases of our series.

[1] Our case 4, a child only $2^1/_2$ years of age and showing a striking skull asymmetry, tends to support this view.



a) b)

Fig. 3. Case 12. a) p. a. view. b) lateral view.
Abnormal diploic channels in the frontal region. In this case there was no calcification.

A closer study of these enlarged vascular channels reveals that they are diploic veins. Widened arterial grooves which occur so frequently with parasagittal and convexity meningiomas, have not been described in connection with STURGE-WEBER syndrome, nor have we ourselves seen them. Normally, the diploic veins, although variable in number, position and form are particularly prominent in the region of the parietal eminence. These vascular trunks in this region combine to give a stellate appearance (described as resembling a »star-fish» figure). When the network of diploic veins is altered in STURGE-WEBER syndrome, trunks both enlarged and abnormally arranged appear. These trunks radiate from a site overlying the lesion.

The presence of these changes in the diploic veins may contribute to localize the site of the lesion in certain cases when calcification is not present. Our case 12 (Fig. 3) is particularly interesting in this respect. There was no calcification in this case. Frontally, however, there was a group of enlarged channels forming a star figure in the P. A. view. (Fig. 3 a.) The right side of the cranial vault was underdeveloped and the right lateral ventricle was a little enlarged. The pathological examination showed a lesion of the STURGE-WEBER type in the right frontal pole.

Calcifications: The details of these have been described by many authors including WEBER (16), DIMITRI (4), MARQUE (12), KRABBE and WISSING (10), BERGSTRAND, OLIVECRONA and TÖNNIS (1), LINDGREN (11).

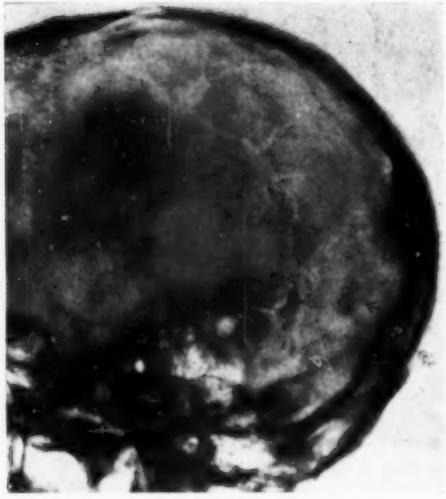


Fig. 4. Case 8. Atypical calcification. An enlarged diploic channel joins the diploic »parietal star» with the site overlying the calcification.

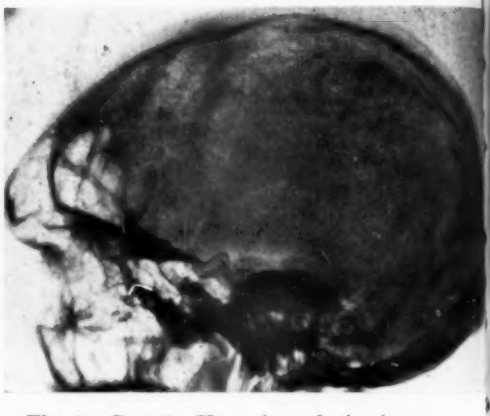
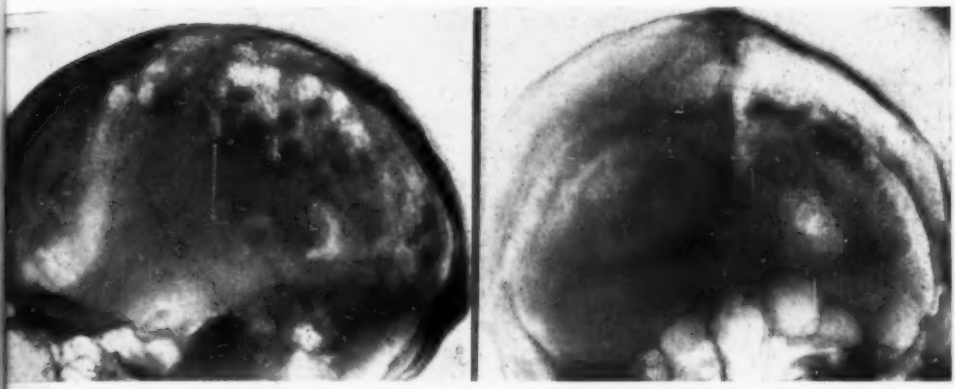


Fig. 5. Case 6. Huge frontal air sinuses. Typical calcification in the occipito-parietal region.

When the calcifications are typical they appear as sinuous, garland-shaped, double contoured lines which follow the often hypoplastic convolutions (microgyria) of the affected cerebral cortex. The commonest localization is the occipito-parietal region. According to HEUBLEIN, PENDERGRASS and WIDMANN (8) the angular and supramarginal gyri in the parietal region are most frequently involved. They are found according to SCHWARTZ (15), in about 80 % of cases. Occasionally they are bilateral.

It is interesting to observe that the sinuous, double-contured calcification is not, of itself, pathognomonic of STURGE-WEBER syndrome. In 1939 LINDGREN (11) described calcification of this type in cases of glioma. This author states, however, that the absence of radiological evidence of raised intracranial pressure as well as the encephalographic findings in STURGE-WEBER syndrome, readily differentiates the calcification found in this condition and that associated with glioma. The presence in the STURGE-WEBER syndrome of skull asymmetry and the altered appearance of the diploic veins can also be used in making the differentiation.

In our material we have found typical calcification in 9 cases. When the calcifications have not the described appearance we call them atypical and such calcifications we have observed in three cases (fig. 4). Two cases presented no calcification. In two cases the calcification was bilateral,



a) b)

Fig. 6. Case 6. Encephalography. a) lateral view. b) p. a. view. Patient prone. Marked dilatation of subarachnoid spaces over left hemisphere. Note that the cortical atrophy is much larger than the calcified zone.

in eight cases it was located in the occipital lobes, in the occipital and temporal lobes in one case, in the occipital and parietal lobes in two cases, and solely in the parietal lobe in one case. Of the unilateral calcifications (10 cases), in seven cases they were on the left side and in three cases on the right side.

In this syndrome, it will be noted, calcareous deposits can always be demonstrated histologically (lying in the outer layers of the cerebral cortex and on the wall of the small vessels) although they sometimes are not radiologically demonstrable. Furthermore, the area of brain affected is generally larger than the extent of calcification shown on the films.

Other peculiarities: Only one case (Fig. 5) in our series shows enlarged frontal air sinuses. This peculiarity has been reported in one case by BROCK and DYKE (2) and in another by MONIZ and LIMA (13). In the latter there was also enlargement of the remainder of the paranasal sinuses. We have never encountered significant enlargement of these other sinuses in our material. We do not regard such changes as peculiar to STURGE-WEBER syndrome.

Encephalography

The authors who have carried out such an examination have found a slight dilatation of the lateral ventricle on the affected side, often more marked in the area corresponding to the lesion. OLIVECRONA states, for example, that he has in two of his cases found: »Eine geringe Über-

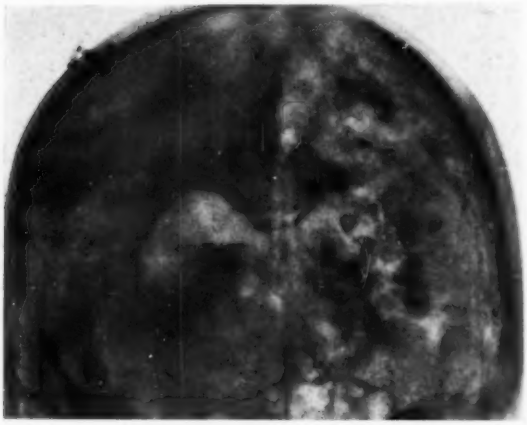


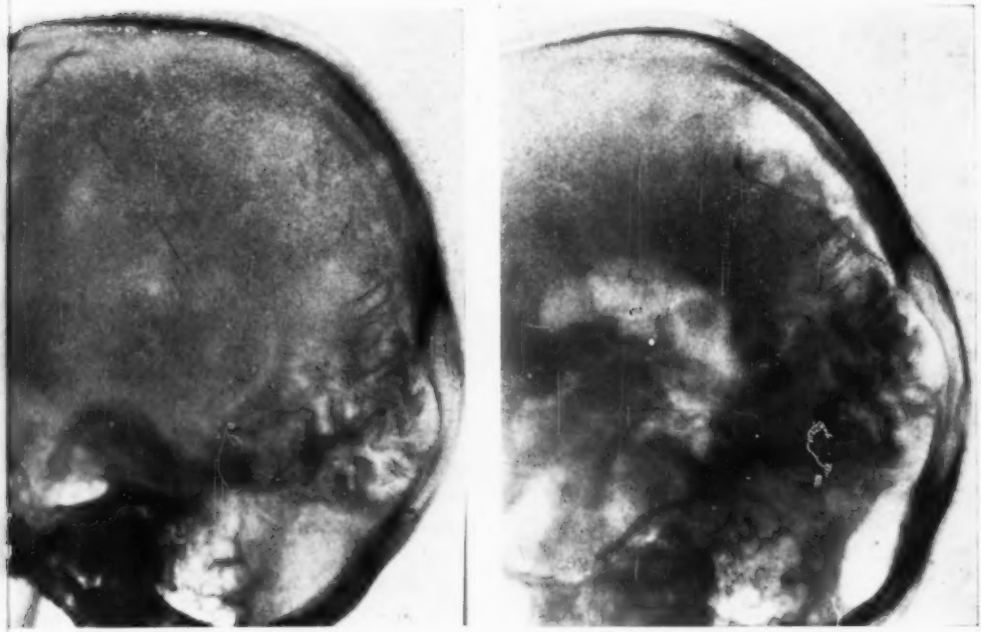
Fig. 7. Case 5. Encephalography. Strikingly widened subarachnoid spaces on the left side. No considerable difference of the two lateral ventricles.

ziehung des Ventrikelsystems nach der Herdseite zu, was als Ausdruck einer Schrumpfung gedeutet wurde.»

In our material there are eleven encephalographies. Four of these show no pathological changes. In five cases there is a slight enlargement of the lateral ventricle on the affected side, sometimes more marked near the lesion. In no case has there been any dislocation of the ventricular system. But, if the findings concerning the ventricular system are generally minimal, more definite evidence can frequently be obtained from a study of the subarachnoid spaces. These are enlarged in six cases of our series and strikingly so in four of them. (Fig. 6.) In two cases the enlargement of the subarachnoid spaces is unaccompanied by any concomitant enlargement of the lateral ventricles (Fig. 7). The widening of the subarachnoid spaces has received but little attention from other authors: we have found it described in one of the two cases of MUSCETTOLA (14) and in the one case of GREEN, FOSTER and BERENS (7). We feel that this change, a result of the microgyria and cortical atrophy, may be an indication of the extent of the malformation which is often, as we have noted above, larger than the calcification would suggest. In our case 2, the routine films revealed calcification limited to the occipital and temporal lobes. The encephalography showed enlargement of the subarachnoid space and widened cerebral sulci over the entire right side of the brain convexity. (Fig. 8 b.) It was found at operation that practically the entire right hemisphere was affected.

Arteriography

Of carotid angiography used in the examination of STURGE-WEBER syndrome OLIVECRONA says: »Die Bedeutung des Arteriograms liegt, soweit



a) b)

Fig. 8. Case 2. a) Preliminary film. b) Encephalography; prone position. Comparison between a) and b) demonstrates that air in the sulci may help to show the calcified atrophic convolutions better.

bis jetzt bekannt ist, hauptsächlich darin, dass Gefässmissbildungen anderer Art ausgeschlossen werden können. In their three arteriographies BERGSTRAND, OLIVECRONA and TÖNNIS found practically no pathological changes. This was also the experience of MONIZ and LIMA in their case. In FURTADO's (5) case, however, there were several small vessels arising from the artery of the angular gyrus, and from the posterior temporal artery, which extended to the site of the calcification. FURTADO refers to »an angiomatous appearance». GREEN has in one case found increased vascularity, and decreased circulation time in the area of calcification, the latter being incorporated in the terminal distribution of the right superior and posterior parietal arteries. He states: In our opinion the diagnosis (of STURGE-WEBER syndrome) may be confirmed if satisfactory stereoscopic angiographic studies can be made, even when calcifications are absent.

Of seven internal carotid angiographies and one external carotid angio-

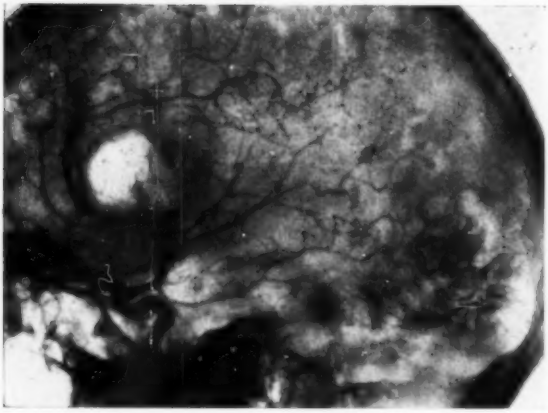


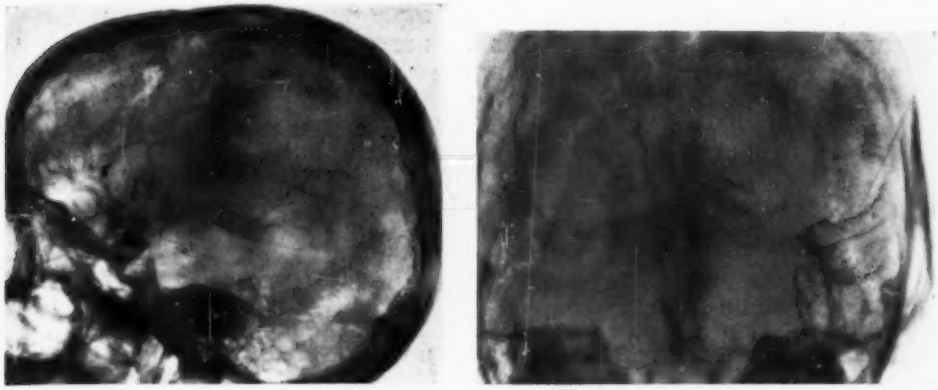
Fig. 9. Case 5. Arteriography. Many small branches of the posterior cerebral artery extend to the calcification. No dilated arteries.

graphy in our material, four are normal. In case No. 5 many small vessels in the area of supply of the filled posterior cerebral artery are present (Fig. 9), but are more suggestive of a normal variant than an angioma. There are no signs of dilated arteries or veins.

Case No. 13 presents the angiographic appearance of an avascular expanding process (Fig. 10). At operation an intracerebral haematoma was found, and only the pathological examination revealed the exact nature of the lesion (STURGE-WEBER with secondary haemorrhage). So far as we know this is the first case reported demonstrating that this type of lesion can cause an intracerebral haemorrhage. In 1906 CUSHING (3) described three cases of facial naevus associated with intracranial haemorrhage, which retrospectively must be classed with STURGE-WEBER syndrome. In these three cases, however, the diagnosis of intracranial haemorrhage was only presumptive, and there was no positive evidence forthcoming.

Case No. 14 shows enlargement of some of the vessels of the left side during the venous phase of the internal carotid angiography. The external carotid angiography of the same side, reveals a somewhat wide middle meningeal artery, but, in our opinion, it cannot be definitely said to be pathological.

With due consideration to the fact that FURTADO's case was a patient aged five years, and therefore considerably younger than MONIZ's patient, the latter states: »Sollten spätere Beobachtungen an Fallen bei jungen Menschen ebenfalls in der Kreislauf eingeschaltete Angiome ergeben, so würde der Fall FURTADO's beweisen, dass in einen frühen Phase der Entwicklung der STURGE-WEBER-KRABBE'schen Krankheit ein echtes Angiom vorhanden ist, das sich mit der Zeit zurückbildet, bis es vollkom-



a) b)

Fig. 10. Case 13. Arteriography.

a) Lateral picture. The branches of the middle cerebral artery are stretched around an avascular zone.

b) A. p. view with the tube angled about 30 degrees cranially. The anterior cerebral artery is displaced to the right.

men erlischt.» There are two carotid angiographies carried out on very young patients (case No. 4 aged $2^1/_2$ and case No. 12 aged 4 in our series. The findings are normal ones.

In our opinion carotid angiography is of value in STURGE-WEBER syndrome in order to exclude other pathological lesions (*e. g.* arteriovenous aneurysms) or in the diagnosis of complications (intracerebral haemorrhage). Possibly a study of the capillary phase (not in use at the Serafimer hospital at the time our patients were examined) may provide more information, especially if the examination of the cerebral circulation be improved by a more extensive use of cinematography.

Undoubtedly the main radiological sign in STURGE-WEBER syndrome is the demonstration of intracerebral calcifications with typical features.

There are, however, other signs revealed by routine skull examination and by encephalography which may be useful in localizing the lesion when no calcification is demonstrable, in the differential diagnosis when the calcification is atypical, and for a more accurate assessment of the extent of the lesion when a typical calcification is present. These signs are: asymmetry of the skull, enlarged and abnormally arranged vascular channels of the vault, enlargement of a part of the lateral ventricle, and the often striking widening of the subarachnoid spaces.

We cannot share the optimism of some authors (*e. g.* GREEN) for carotid angiography. Nevertheless we must acknowledge that carotid angiography is useful in excluding other pathological lesions (*e. g.* arteriovenous aneurysms) and in the diagnosis of complications (intracerebral haemorrhage). Angiography furnishes little information however concerning the nature of the process or its localization.

SUMMARY

The authors have studied the radiological features of 14 cases of STURGE-WEBER syndrome. Typical calcification was found in nine cases, atypical in three, and no calcification in two. Other findings of diagnostic and theoretical value are: asymmetry of the skull, enlarged and abnormally arranged vascular channels of the vault, enlargement of a part of the lateral ventricles, and widening of the subarachnoid space. Carotid angiography may be useful only in order to exclude other pathological lesions, *e. g.* arteriovenous aneurysms, or in the diagnosis of such complications as intracranial haemorrhage.

ZUSAMMENFASSUNG

Die Autoren haben die radiologischen Kennzeichen von STURGE-WEBER'schen Syndrom an vierzehn Fällen studiert. Typische Verkalkung fand sich in neun, atypische in drei und gar keine in zwei Fällen. Weitere Ergebnisse von diagnostischem und theoretischem Wert sind: Asymmetrie des knöchernen Schädels, erweiterte und abnorm gelagerte Gefässfurchen im Schädeldach, Vergrösserung von Teilen der Seiten-Ventrikel und Erweiterung der Subarachnoidal-Räume. Carotis-Angiographie sollte nur Anwendung finden zum Ausschluss weiterer pathologischer Veränderungen z. B. des arteriovenösen Aneurysma oder zur Diagnose von Komplikationen z. B. intracranieller Hämorrhagie.

RÉSUMÉ

Les auteurs ont étudié les données radiologiques ressortant de 14 cas présentant le syndrome de STURGE-WEBER. Il y avait des calcifications typiques dans 9 cas, atypiques dans 3 cas et aucune calcification dans 2 cas. D'autres signes d'importance théorique et diagnostique sont: l'asymétrie du crâne, la vascularisation accrue et abnorme de la voûte, l'élargissement d'une partie des ventricules latéraux et la dilatation de l'espace subarachnoïdien. L'angiographie carotide ne sert qu'à exclure d'autres lésions telles que l'anévrysme artério-véneux ou à rechercher des complications telles que l'hémorragie intracranienne.

REFERENCES

1. BERGSTRAND, H., OLIVECRONA, H., und TÖNNIS, W.: Gefässmissbildungen und Gefässgeschwülste des Gehirns. Thieme, Leipzig, 1936.
2. BROCK, S., and DYKE, C. G.: Venous and arterio-venous angiomas of brain: clinical and roentgenographic study of 8 cases. Bull. Neurol. Inst. New York. 2 (1932), 247.
3. CUSHING, H.: Cases of spontaneous intracranial haemorrhages associated with trigeminal naevi. J. A. M. A. 47 (1906), 178.

4. Dimitri, V.: Tumor cerebral congenito (angioma cavernosum). Rev. Asoc. med. argent. 36 (1923), 63.
5. Furtado, D.: quoted by Moniz.
6. Green, J. R.: Encephalotrigeminal angiomatosis. J. Neuropath. and exper. Neurol. 4 (1945), 27.
7. Green, J. R., Foster, J., and Berens, D. L.: Encephalotrigeminal angiomatosis (Sturge-Weber syndrome). Am. J. of Roentgenology and R. Therapy. 64 (1950), 341.
8. Heublein, G. W., Pendergrass, E. P., and Widmann, B. P.: Roentgenographic findings in neurocutaneous syndromes. Radiology. 35 (1940), 701.
9. Krabbe, K.: Facial and meningeal angiomatosis associated with calcifications of brain cortex. Arch. Neurol. and Psychiat. 32 (1934), 737.
10. Krabbe, K., and Wissing, O.: Calcifications de la pie-mère du cerveau (d'origine angiomateuse) démontré par la radiographie. Acta Radiol. 10 (1929), 523.
11. Lindgren, E.: Über corticale Verkalkungen im Gehirn. Der Nervenarzt. 3 (1939), 138.
12. Marque, A.: Consideraciones sobre angiomas en la infancia. Rev. oto-neuro-oftal. 1 (1927), 202.
13. Moniz, E.: Die cerebrale Arteriographie und Phlebographie. Berlin, 1940.
14. Muscettola, G.: La malattia di Sturge-Weber. La Radiol. med. 33 (1947), 534.
15. Schwartz, C. W.: Vascular tumours and anomalies of skull and brain, from roentgenologic viewpoint. Am. J. of Roentgenology and R. Therapy. 41 (1939), 881.
16. Weber, F. P.: Right-sided hemi-hypotrophy resulting from right-sided congenital spastic hemiplegia, with a morbid condition of the left side of the brain, revealed by radiograms. J. Neurol. and Psychopath. 3 (1922), 134.

FROM THE KING GUSTAF V:S JUBILEE CLINIC (DIRECTOR: DR BERTIL EBENIUS), LUND, SWEDEN.

VERTEBRAL HEMANGIOMA WITH COMPRESSION OF THE SPINAL CORD[1]

Report of a case treated with roentgen with good clinical results

by

Inge Lindqvist

Nothwithstanding the fact that investigations of large series of autopsy material chosen at random show that vertebral hemangioma occurs with a frequency of 10 to 12 per cent, these growths seldom reach such a size as to cause clinical signs. It is nevertheless important that the clinician and the roentgenologist should bear in mind the possibility of hemangiomata when diagnosing cases of compression myelitis.

A survey of the literature reveals that the disease has attracted increasing interest during recent years. For example, SCHEEL's (37) study in 1939 on cases of hemangioma of the vertebra with clinical signs and confirmed diagnoses included but 36 cases. Only a few years later — in 1943 — BLACKFORD's (3) paper includes almost double that number, and a not inconsiderable number of cases have been added since that time.

In the majority of the cases described hitherto the treatment has been surgical or perhaps both surgical and radiological. Cases treated with roentgen therapy only, on the other hand, have been few and far between. FOSTER and HEUBLEIN (8) reported in 1947 that there were not more than 14 of these cases altogether.

The macro- and microscopical anatomy of vertebral hemangioma has been described in detail and therefore requires no mention at this stage.

The roentgen picture presents a characteristic appearance corresponding to the anatomical conditions. The most typical signs are trabeculae of increased bone density contrasting with intervening areas of

[1] Submitted for publication, Sept. 15, 1950.

reduced density. The trabeculae are arranged mainly as parallel vertical columns, which may be connected by narrower horizontal bands. At times these striated or net-like markings are less regular and are replaced by small vacuoles situated close together and giving a striped appearance. The form of the vertebrae is sometimes retained but often the margins are pressed outward by the pathological tissue. Occasionally the vertebrae may be more or less collapsed and their upper and lower limits may even be concave. When the vertebral arches and apophyses are involved they may retain their shape or become deformed, widened and thickened. In such cases the striated markings frequently appear as cystiform reductions. The intervertebral discs are generally intact.

Clinical symptoms: Hemangioma of the vertebrae may give rise to symptoms ranging from tenderness and pain around the involved vertebrae to pronounced neurological disturbances. In the presence of marked growth and enlargement of the spinal column or of epidural penetration, hemangioma may cause severe conditions including even the typical picture of complete transverse lesion of the spinal cord. The three following categories can be defined according to the presence or absence of subjective or objective symptoms:

1) Hemangioma without clinical symptoms discovered by accident on roentgenologic examination of the thoracic or abdominal organs. These tumors due to their benign character require no treatment. They show very little tendency to further growth and clinically usually remain indolent.

2) Vertebral hemangioma with symptoms in the form of local tenderness and pain or radiating pain, but without objective signs of nerve injury.

3) Vertebral hemangioma with both subjective and objective symptoms of compression myelopathy.

To the three foregoing groups FOSTER and HEUBLEIN (8) have added a fourth to cover hemangiomas of the vertebrae which show fractures with or without myelopathy. This condition is said to be rare by these and other workers. The effect on the strength of the vertebrae of hemangioma is the matter of dispute. HOLTA (15) et al. described cases of trauma with fractures of the hemangiomatous vertebrae. GRIEP (13), on the other hand, describes a case of fracture of the eighth and twelfth thoracic and the second lumbar vertebrae, which were otherwise healthy, while the third lumbar vertebra was undamaged, even though it showed the changes characteristic of hemangioma.

As regards diagnosis the clinical picture suggests the nature of the condition in the spinal cord but it is the characteristic roentgen appear-

ance which gives the exact diagnosis owing to the usually typical roentgen picture. As far as the differential diagnosis is concerned, metastases and tuberculosis are said to be the two conditions most frequently considered, although a tuberculous lesion will involve both the bone and the cartilage. Vertebral fractures with general decalcification and syphilis may produce similar roentgen pictures.

The prognosis is poor if objective signs of compression of the spinal cord develop and no treatment is given. It is said that all cases which have reached this stage will, if left alone, end fatally within a few months or years.

Surgical or radiological treatment or a combination of both have been carried out.

In surgical intervention the spinal apophyses and vertebral arches are removed and the pressure on the spinal cord caused by the expansive tissues is reduced or eliminated. Those before mentioned parts of the vertebrae involved by the tumors may be removed, and in the same manner the angiomatous tissue penetrating into the epidural layer may possibly be reached and extirpated. A hemangioma occurring in the vertebral bodies themselves canno be removed surgically, but even in such cases good effect upon the clinical symptoms is obtained by the operation relieving the pressure. The results of surgical treatment are highly dependent upon control of the severe hemorrhages associated with the operation. The primary mortality is very high.

The effects of radiation, which previously were regarded as unsatisfactory, appear to have grown considerably more encouraging during recent years, as evidenced by reports of several cases with good results (FOSTER and HEUBLEIN (8), JUNGHAGEN (18), SCHEEL (37), et al.).

This change in confidence in the possibility of attaining good results with irradiation only is well illustrated by the following statements, published at an interval of only two years. In 1940, STEHR (38) in summarizing experiences up to that time, wrote that since there was no report of spontaneous healing in such cases and since truly encouraging effects of radiation had never been observed, nothing remained but to recommend operation in all cases of vertebral hemangioma with compression myelopathy. Contrasting with STEHR's conclusion, we find a report by FERBER and LAMPE (7) in 1942 to the effect that roentgen therapy is the method that should be considered, at least in the beginning.

The case of vertebral hemangioma with compression symptoms to be described in the following appears further to confirm that radiologic treatment alone may lead to good results.

Fig. 1.

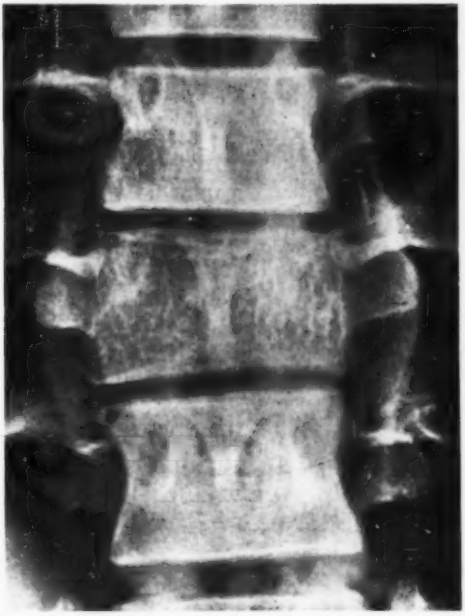


Fig. 2.

Case Report

An 18-year-old bricklayer was treated at the Jubilee Clinic in Lund in 1938 and 1939 and thus has been under observation for ten years at the time of writing.

The patient developed weakness and numbness in the legs and an uncertain gait in April 1938.

The first examination in June 1938 revealed spasticity in the legs, hyperactive patellar and achilles tendon reflexes, absence of abdominal reflexes, as well as positive protein reaction in the spinal fluid. The gait was spastic and the feet kept wide apart. The preliminary diagnosis was multiple sclerosis.

The patient grew rapidly worse and by September 1938 he had pronounced spastic paresis of both legs, which he could scarcely lift when lying down. There was great impairment of all modalities of sensation below the umbilicus. He could not feel changes in position of the big toes and was unable to walk.

Examination of the spinal fluid revealed an initial pressure of 120 mm of water. There was complete manometric block on the Queckenstedt manœuvre; there were small reactions on respiration. The final pressure was 20 mm. The Pandy reaction was two plus, the Nonne reaction one plus. There were three lymphocyte cells per cubic millimeter.

Since a roentgen examination showed changes in the ninth thoracic vertebral body indicating hemangioma, the patient was referred by the neurosurgeon to the Jubilee Clinic in Lund.

On admission to this clinic the condition was as above described.

Fig. 3.

Fig. 4.

A supplementary roentgen examination was made at the Roentgen Diagnostic Department in Lund, at which time other parts of the skeleton were also roentgenographed. The findings may be summarized as follows:

Roentgen examination showed bone changes in the ninth thoracic vertebra and in the right ischium, corresponding to cavernous hemangioma. The process extended within the ninth thoracic vertebra beyond the boundaries of the vertebral body and bulged into the spinal canal and also laterally and anteriorly into the soft parts. (H. Hellmer.) Fig. 1—3.

The patient was given roentgen treatment in November 1938 and in January, April and August 1939 (Professor L. Edling). Improvement was noted during the very first week of treatment and continued steadily thereafter. The treatments were administered as follows:

Roentgen treatment was given to five fields — three dorsal and two ventral. The estimated tumour dose was about 2,100 r. In addition a roentgen dose of about the same magnitude was given to the hemangioma in the ischium. This had given no manifestations other than the roentgenological ones.

In August 1939 when the patient was given the last series of roentgen treatments, it was noted that he still had mild numbness of the feet, as well as some insecurity of balance, although the latter was not constant. Otherwise he had no symptoms. He could walk »any distance» and he had cycled about 90 miles in one day with no trouble. The motility and sensibility were normal, the patellar and achilles tendon reflexes were still hyperactive, and there was clonus of the feet. The abdominal reflexes had returned to some extent.

Myelography was done for the first time in March 1940. It revealed a moderate, relative block in the anterior area of the spinal canal at the level of the ninth thoracic ver-

tebra. However, the contrast fluid was able to pass the obstacle in a thin band 3 mm. in breadth. Fig. 4.

The condition continued to improve and examination in July 1948 revealed the following:

Subjective: Occasionally there was very slight numbness of the feet, but otherwise there were no symptoms. The patient was able to work as a bricklayer without trouble.

Objective: Motility and sensibility were normal. The patellar and achilles tendon reflexes were still hyperactive and there was a suggestion of clonus in the feet. The abdominal reflexes could be elicited in both upper quadrants. The gait was normal.

Roentgen examination on July 10, 1948: Spinal column: the hemangioma in the body of the ninth vertebra had the same appearance as in October 1938. The height of the vertebral body was unchanged. As at the previous examination, it was found that, in addition to the altered structure of the vertebral body, the vertebra was somewhat distorted in shape, being slightly lower and wider in the frontal plane than normal. The vertebral body was surrounded by a mild spindle-shaped swelling of the soft parts. This swelling was somewhat narrower than at the examination in November 1938. Pelvis: the hemangioma in the proximal part of the inferior part of the right ischium had the same appearance as at the first examination in 1938 (Olle Olsson).

SUMMARY

A case of a vertebral hemangioma and of a hemangioma in the pelvis with pronounced neurologic signs of compression of the spinal cord was treated with irradiation only. The patient became free from neurologic symptoms with the exception of a mild residual spasticity and has since the treatment 1938—39 had complete working capacity.

ZUSAMMENFASSUNG

Ein Fall mit Hämangiom der Wirbelsäule und des Beckens, der deutliche neurologische Zeichen für eine Kompression des Rückenmark-Stranges aufwies, wurde allein mit Bestrahlung behandelt. Mit Ausnahme von einer zurückbleibenden leichten Spastizität wurde der Patient von den neurologischen Symptomen befreit. Er ist seit der Behandlung im Jahre 1938—39 voll arbeitsfähig.

RÉSUMÉ

Un cas d'hémangiome vertébral avec une localisation au niveau du pelvis provoquant des symptômes neurologiques prononcés de compression de la moelle épinière a été traité uniquement par radiations. Le malade a été libéré de tous ses symptômes neurologiques à l'exception d'une légère spasmodie résiduaire, et, depuis le traitement 1938—1939 sa capacité de travail a été entière.

REFERENCES

1. Alpers, B. J. & Pancoast, H. K.: Surg., Gynec. & Obst. 55 (1932), 374.
2. Bailey, P. & Bucy, P. C.: J. A. M. A. 92 (1929), 1748.
3. Blackford, L. M.: J. A. M. A. 123 (1943), 144.
4. Bucy, P. C. & Capp, Ch. S.: Am. J. Roentgenol. 23 (1930), 1.
5. Clavelin et Gauthier: Rev. de Chir., Paris. 51 (1932).
6. Deetz: Ges. für Natur- und Heilkunde, Dresden. 23 (1901). (Quoted in München. med. Wochenschr. 48 (1901), 1506.)

7. Ferber, L. & Lampe, I.: Arch. Neurol. and Psychiat, volume 47 (1942).
8. Foster, D. & Heublein, G. W.: Am. J. Roentgenol. 5 (1947).
9. Gatti-Casazza, A.: Atti Soc. Lomb. Chir. 5 (1937), 1172.
10. Gerhardt, D.: Deutsche Ztschr. f. Chir. 6 (1895), 127.
11. Globus, J. H. & Doshay, J. L.: Surg. Gynec. & Obst. 48 (1929), 345.
12. Gold, E.: Arch. f. klin. Chir. 139 (1926), 729.
13. Griep, K.: Röntgenpraxis 14 (1942).
14. Guillain, G., Decourt, J. & Bertrand, J.: Ann. méd. 23 (1928), 5.
15. Holta, O.: Acta radiol. 23 (1942), 423.
16. Ireland, J.: Am. J. Roentgenol. 28 (1932), 372.
17. Jiano, J., Grigoresco, D. & Vasiliu, D.: J. de chir. 38 (1931), 652.
18. Junghagen, S.: Acta radiol. 28 (1947), 715.
19. Junghanns, H.: Arch. f. klin. Chir. 169 (1932), 321.
20. — Ibid. 169 (1932), 204.
21. Koch-Grunberg, E.: Inauguraldissertation, Giessen, 1936.
22. Lamy, L. & Weissmann, L.: Revue d'orthop. 23 (1936), 121.
23. Lièvre, J. A.: Bull. et mém. Soc. méd. d. hôp. de Paris 1932: 896.
24. — Presse méd. 52 (1934), 1571.
25. Livingston, S. K.: Am. J. Roentgenol. 33 (1935), 381.
26. Makrycostas, K.: Virchows Arch. f. path. Anat. 265 (1927), 259.
27. — Arch. f. klin. Chir. 155 (1929), 633.
28. Michon, M. M. P., Gregoire et Lafont, J.: Rev. neurol. I (1935), 565.
29. Muthman, A.: Virchows Arch. f. path. Anat. 172 (1903), 324.
30. Nemours-August: Société radiologie médicale, 22 (1934).
31. Perman, E.: Acta chir. Scandinav. 61 (1926), 91.
32. Pfahler, E.: Radiology 46 (1946).
33. Pierson, J. W., Farber, G. & Howard, J. E.: J. A. M. A. 116 (1941), 2145.
34. Ribbert, Ref. Deutsche med. Wchnschr. 38 (1912), 390.
35. Roederer, C.: Paris méd. 87 (1933), 544.
36. Sandahl, C.: Acta chir. Scandinav. 69 (1932), 63.
37. Scheel, A.: Nord. med. 1 (1939), 854.
38. Stehr, L.: Fschr. Röntgenstrahlen 62 (1940), 179.
39. Stern, A.: Monatschr. f. Psychiat. u. Neurol. 104 (1941).
40. Trommer, B.: Frankfurt. Ztschr. f. Path. 22 (1919/20), 313.

FROM THE VASA HOSPITAL (DIRECTOR: DR. BO EWERT) AND THE ROENTGEN DEPARTMENT II (DIRECTOR: DR. CARL JOHAN HANSSON) OF SAHLGRENS HOSPITAL, GÖTEBORG, SWEDEN.

NEUROSARCOMA DUODENI[1]

by

Allan Elliot and *Carl Johan Hansson*

Introduction

Primary malignancy of the small bowel is present in about 1 ‰ of all sections (12). Most of these cases are those of carcinoma and FRANK & al. estimate the number of cases of sarcomata of the small intestine described in literature up to 1942, at about 350.

In a revue of about 250 sarcomata of the small bowel SHALLOW & al. found 5 % to be duodenal sarcomata. BOYCE & MCFETRIDGE mention that PERRY & SHAW did not find more than 6 cases among about 18,000 sections at Guy's Hospital. According to KOCK's investigation of cases operated upon for sarcoma of the small intestine at all the surgical clinics in Stockholm during the first four decades of this century, there is one case of sarcoma duodeni.

FRASER, CEDERMARK and others point out that it is very difficult to determine which type of sarcoma is the most frequent in the small intestine. The nomenclature of earlier days was rather vague and even nowadays the difficulties of microscopic differentiation of the immature forms are considerable.

COHN & al. consider that the lympho-, fibro- and leiomyosarcomata are the most frequent. FRANK believes that the future will provide more malignant neurosarcomata and he himself describes 2 cases, neither of which is situated in the duodenum. Anyhow, CEDERMARK had one case and ROSE has written of a neurinoma duodeni without signs of malignancy.

The microscopic picture of neurinoma is characteristic — with the palisadical formation of the cellular nuclei. The macroscopic one is less typical. FORSSMAN and others (8, 10) show that the centres of intestinal sarcomata are in general very often necrosed; consequently the intestinal wall will sometimes rupture if only a thin membrane is left between the tumour and the intestinal cavity, which will thus com-

[1] Submitted for publication, Nov. 2., 1950.

municate directly with the liquefied part of the former. The result is thus the formation of a crater and the enlargement of the bowel asymmetrically. The tendency to ulceration can make the differential roentgen diagnosis between sarcoma and cancer impossible. An annular growth is said to be usual.

CEDERMARK's neurosarcoma presents signs of ulceration and WEBER & KIRKLIN have shown a photograph of a myosarcoma duodeni, having an appearance very like that of our own case. Both RAGIN's & SHIVELY's and CEDERMARK's cases have multiple liver metastases.

The clinical symptomatology has few characteristics. Naturally a peripapillar sarcoma duodeni may cause early icterus but those situated supra- or infrapapillary are »silent» for a long time and produce diffuse pain in the right hypochondrium. BOYCE & MCFETRIDGE point out that the patient's abdominal symptoms at a late stage are less marked than in cases of carcinoma or benign ulcerations. Perforations have only occurred as far as is known a few times (8). Signs of stenosis should be somewhat rare, for the sarcomata usually grow out centrifugally into the mesenterium and do not obstruct the intestinal canal. Ileus of the ileum and the jejunum arises from kinking and intussusception, which does not occur in the retroperitoneally-situated duodenum.

Only one diagnosis before operation out of 17 cases at the Mayo Clinic was correct (13). To cite BOYCE & MCFETRIDGE »we are all wise after such a case but, it is too much to expect that the diagnosis could have been made in the first case ever seen and, on the laws of probability, there will probably never be a second chance». But if the possibility of duodenal malignancy crosses one's mind, perhaps ENGESET's investigation of the duodenal content via a duodenal tube may provide some information as in his case of cancer duodeni (not yet published — personal communication).

The prognosis of the duodenal sarcoma is naturally bad and worse than that of the other intestinal sarcomata (12). Probably this fact is associated with the greater surgical difficulties of radical extirpation in the duodenal area; possibly with the symptomless course of the early stages of the disease. On the other hand the outlook for the patient with duodenal cancer is graver than with duodenal sarcoma, because sarcomata in general are more radiosensitive (6).

Anyhow, this sensitivity varies considerably. BOYD states that the neurosarcoma is quite resistant to roentgen therapy. BOYCE & MC FETRIDGE recommend surgical interference on wide indications and DIXON & al. mention modern radical operative procedures such as combined duodenectomy, partial ectomy of the ventricle, the pancreas, the choledochus and, if necessary, the jejunum; and choledochojejunostomy.

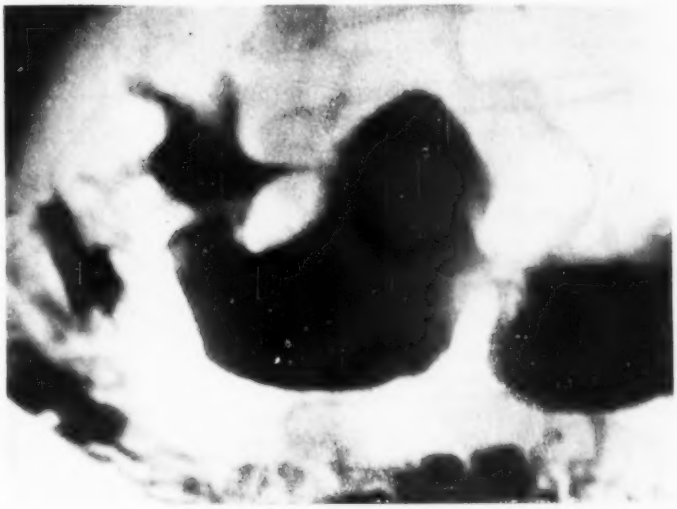


Fig. 1.

Case Report

History. G. D. G., 62, electrician, 40 years at sea, was admitted to the Vasa Hopsital in Jan. 1949, complaining of pain in the legs, not unlike the syndrome of claudicatio intermittens. Upon examination he was found to have bilateral flat feet and this was corrected by simple orthopedic measures. Anyhow, the patient had also complained of »considerable» loss of weight during the last few months but said that he felt quite well and denied any form of abdominal trouble.

The past history was irrelevant.

Physical examination. Temperature, normal. He was well developed, rather thin without any signs of recent loss of weight. Skin colour healthy. No changes in the heart or lungs. The abdomen was quite normal and the liver not palpable.

Laboratory findings. Wasserman, Kahn and Meinicke reactions negative. Sedimentation rate 10 mm/one hour; red blood cell count 4 millions per cubic millimeter. Haemoglobin — 79 %. The stools some times contained minimal traces of blood (Weber's reaction green), most tests being negative even as late as May 1950, when the patient still had no anaemia.

No other changes occurred during the progress of the disease.

Roentgen examination. Jan. 1949: The bulbus duodeni was deformed, with a probable niche; it was more rigid than in cases of simple ulceration (malignant?). See Fig. 1.

14 days later, after ambulatory dietetic treatment an area of erosion with raised margins as large as the distal end of the thumb was noted in the bulbus duodeni.

Operation. Febr.: at Ekman's Hospital (Dr. Viktor Henriksson).

Exploratory laparotomy: Midline epigastric incision. On the curvatura ventriculi major some deep red lymph nodes; one removed for microscopic examination. About 4 centimetres distal to the pylorus was a tumour lying in the duodenum and spreading on to the pancreas. Metastases were present in the liver at the site of the gall-bladder.

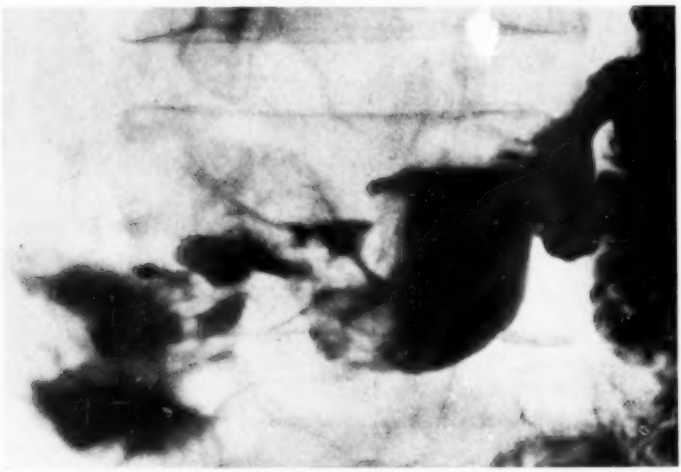


Fig. 2.

By reason of this involvement and of the difficulties of radical extirpation (the head of the pancreas would have had to be removed), nothing further was done.

Macroscopic appearances were those of a highly vascular sarcoma. Because of the palpable crater, however, a surgical diagnosis of carcinoma was made.

After the operation the patient developed a thrombosis in one leg; this cleared up after anti-prothrombin treatment.

A pathological examination of the extirpated lymph gland showed nothing more than a non-specific inflammation.

Postoperative progress. In March anti-syphilitic treatment was commenced, because the diagnosis of a carcinoma still was more or less guess-work and the possibility of a gumma — in spite of negative Wassermann reactions — must be considered in disease occurring in seamen. After a month of suitable treatment the infiltration of the duodenal wall had increased and consequently venereal disease could confidently be excluded.

Towards the end of April the patient developed acute pneumonia which rapidly cleared up with penicillin.

In May the progress of the duodenal lesion was still being controlled roentgenologically. The surgeon had already discussed the possibility of a sarcoma and a series of test roentgen treatments in a field covering the duodenum, were carried out. These were continued intermittently until December when the patient's general condition deteriorated considerably. The roentgen series were all very short because the patient rapidly became exhausted. The total dose administered was 8,100 r.

In the middle of May the patient was sent home for a change and he even started work for a short time as controller.

In July he returned to the Vasa Hospital, which he never left. He was tired but not in bad condition. He had lost weight but within the next two months he nearly regained the loss of half a year (4½ kilograms) and felt fairly well.

When roentgenogram examination in September showed that the round defect of the bulbus had decreased considerably, the probability of a duodenal sarcoma seemed to us to be confirmed empirically. See Fig. 2.

Fig. 3.

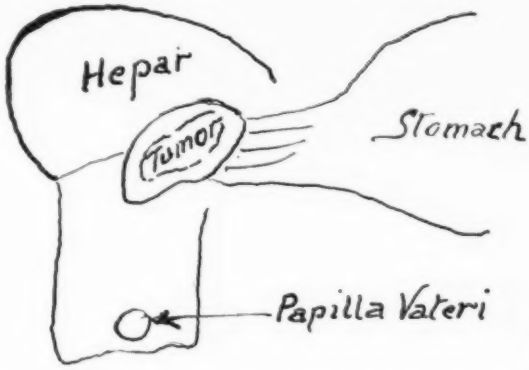


Fig. 4.

In October the patient grew worse, lost weight and grew tired again. From now on the progress of his malady was unbroken. For the first time he developed pain, sometimes of such a degree that narcotics were necessary, in the right hypochondrium, and a mass, as large as an orange, was palpated in the region of the duodenum. The final series of roentgen treatments appear to cause the tumour to some degree to diminish in size.

The last three quarters of the last year of the patient's life were characterzied by marked loss of appetite, an occasional burning pain in the upper part of his abdomen and a slowly increasing size of the liver which finally occupied the larger part of the right side of the abdomen. In September 1950 he died, extremely cachectic and oedematous.

Pathologic report. (From the Pathologic Department of Sahlgren's Hospital, dr. G. VEJLENS.)

Macroscopy: An ulcerating tumour is situated behind the duodenum (see Fig. 3); it is about as large as the palm of the hand and is surrounded by rolled edges. Not more than 1 centimetre of the mucosa is free from invasion — not connected with the pancreas, the papilla of Vater or the choledochus. The liver is greatly enlarged and full of metastases; no metastases seen elsewhere.

Microscopy: The duodenum contains a tumour, arising from the subserosa and growing inwards. Most of its parts resemble the musculature of the duodenal wall and cause atrophy of the mucous membrane merely by pressure. It grows diffusely through the mid-region of the duodenal wall, the inner wall of which is here necrosed. The most

mature parts of the tumour are built up of thin spindle cells, arranged in palisades; in the other parts, the architecture is more irregular. Cellular polymorfism and many atypical mitoses are present.

Microscopic diagnosis: neurinoma malignum.

Comment

The diagnosis of duodenal malignancy was established by the first two roentgenological examinations but a clinical effort to define the type of malignant tumour did not succeed. The final clinical diagnosis was certainly that of a sarcoma but the conclusions were incorrectly drawn. As previously mentioned, the neurosarcoma is more or less roentgen resistant and the indubitable effect of such a treatment in our case is explained by its influence upon the inflammatory element in the large ulceration tumour.

SUMMARY

A case is reported of neurosarcoma (syn.: schwannoma, neurinosarcoma) of the duodenum with an early roentgenologic diagnosis of malignancy. The difficulty of clinical differentiation between carcinoma and sarcoma is pointed out.

ZUSAMMENFASSUNG

Es wird über einen Fall von Neurosarcom (syn: Schwannoma, Neurinosarcoma) des Duodenums berichtet, bei dem röntgenologisch die Frühdiagnose der Malignität gestellt wurde. Die Schwierigkeit der klinischen Differentialdiagnose zwischen Carcinom und Sarcom wird betont.

RÉSUMÉ

Un cas de neurosarcome (synon. schwannome, neurinosarcome) au niveau du duodénum dans lequel le diagnostic radiologique précoce de malignité a pu être établi. Les auteurs rappellent la difficulté qu'il y a à séparer le cancer du sarcome en clinique.

REFERENCES

1. Boyd: Textbook of Pathology, Lea & Febiger, Philadelphia 1940, p. 311.
2. Boyce & McFetridge: Internat. Surg. Digest. 17 (1934), 131.
3. Cedermark: Nord. med. 34 (1947), 944.
4. Cohn, Landy & Richter: Arch. Surg. 39 (1939), 647.
5. Dixon, Lichtman, Weber & McDonald: Surg., Gynec. & Obst. 83 (1946), 83.
6. Forssman: Acta radiol. 24 (1943), 343.
7. Frank, Miller & Bell: Ann. Surg. 115 (1942), 544.
8. Fraser: Brit. J. Surg. 32 (1944—1945), 749.
9. Kock: Acta Chir. Scandinav. 89 (1943), 37.
10. Ragins & Shively: Am. J. Surg. 47 (1940), 96.
11. Rose: Aust. N. Zealand J. Surg. 19 (1949), 163.
12. Shallow, Eger & Carty: Am. J. Surg. 59 (1945), 372.
13. Weber & Kirklin: Am. J. Roentgenol. 47 (1942), 243.

FROM THE ROENTGEN DEPARTMENT (DIRECTOR: PROF. ÅKE ÅKERLUND) OF KAROLINSKA SJUKHUSET, STOCKHOLM, SWEDEN

THE EFFECT OF VARIOUS FACTORS ON THE ROENTGENOLOGICAL DETERMINATION OF THE CARDIAC VOLUME[1]

by

Sven Roland Kjellberg, Henrik Lönroth and *Ulf Rudhe*

Introduction

The object of the present investigation was to test the accuracy of the method for the determination of the cardiac volume described by LARSSON & KJELLBERG (1948) and by KJELLBERG, RUDHE & SJÖSTRAND (1949). A study was therefore made of the following factors that could be expected to affect the accuracy: (1) those connected with the roentgen projection (magnification and plane of projection), (2) those implying individual variations in the shape and position of the heart and (3) those affecting the size, position and shape of the heart in the same individual, such as the phase of respiration and of the cardiac cycle, and the position of the body.

Method

The forementioned method for determination of the cardiac volume requires the subject to be placed in the prone position over a casette holder with two planes, one for postero-anterior and one for lateral projection. Small lead pellets, equidistant from each other, are inserted in the casette holder, thus affording a simple means of correcting the magnification. The postero-anterior projection is taken with the tube angled 30 degrees towards the feet. In both projections the perpendicular distance between the focus and the film is 125 centimeters.

For the statistical calculations, use was made of methods generally known, described by CRAMÉR (1949) and by FISHER (1948) amongst others.

[1] Submitted for publication, Jan. 31, 1951.

In the present investigation, a difference was denoted as probable if the corresponding p value was less than 5 per cent but more than 1 per cent, a significant difference denoting a p value less than 1 per cent.

For further details, reference is made to the relevant sections of this paper.

Material

The material was composed as follows:

1. 140 army volunteers between the age of 18 and 20 years. All underwent a physical examination and were found to be in good health.

2. 87 persons — 67 men and 20 women — between 16 and 60 years of age, with various occupations. An examination of the circulatory organs was made in every case to exclude the presence of any pathological conditions. Fifteen of the men and 9 of the women were in good physical training.

3. 52 persons attending the medical out-patients' department of Karolinska sjukhuset. They were used, in addition to those enumerated under 1 and 2, for determinations of the standard error of a single determination.

Angulation

In a study of the hearts of cadavers, LARSSON & KJELLBERG found that the cardiac volume could be determined with sufficient accuracy by using a roentgenogram in two projections at right angles to each other. The following formula was used:

$$V = F \cdot lbd,$$

where V is the volume in milliliters, l and b the diameters in centimeters, corrected for the magnification, of the postero-anterior projection, whose contour was completed freehand. l is the greatest longitudinal diameter of the ellipse-shaped figure, and b the greatest diameter perpendicular to it. d is the greatest diameter in centimeters of the lateral view corrected for the magnification. F is a variable function of $\frac{d^2}{lb}$. This function was determined empirically.

The forementioned study showed that »very flat» hearts — *i. e.*, those with extremely low values for $\frac{d^2}{lb}$ — had approximately 10 per cent higher values for F than hearts with low values for the same quotient. In the case of »ordinary» hearts, the value of F was found to correspond approximately to that of an ellipsoid $\left(\frac{\pi}{6}\right)$.

On the basis both of the ellipsoid hypothesis put forward by KAHLSTORF and of the results obtained empirically by LARSSON & KJELLBERG, there is reason to assume that the conditions are somewhat more complicated when an oblique projection is used. An attempt will be made in the following to ascertain the effect of the angulation on the factor F and the bases on which the cardiac volume can be calculated. The reasons will first be given for the use of the oblique projection.

From a practical point of view, the angulation is warranted by the fact that the contours of the heart appear more clearly than with the use of rays falling perpendicularly. The lower contour, in particular, stands out considerably more distinctly on well-exposed roentgenograms. This reduces the risk of a purely subjective estimation of the position and appearance of the cardiac border with a corresponding degree of individual variations. 29 persons, aged between 20 and 80 years, were selected at random and photographed in the upright position without angling the tube. Measurements with an ordinary map-measurer showed that, on an average, 42 per cent of the whole cardiac contour was clearly visible on the roentgenogram. In a similar series, photographed in the prone position and with an angulation of the tube of 30° towards the feet, on an average 60 per cent of the total periphery was visible.

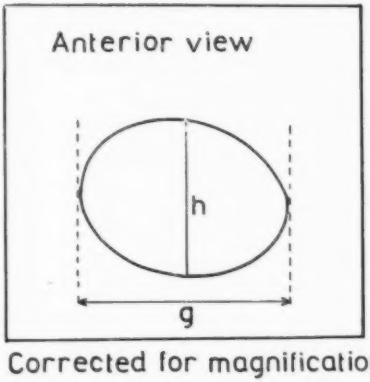


Fig. 1. Anterior view of the heart, using divergent rays with the central rays oblique to the film.

The calculation of the cardiac volume can be made with the help of two roentgenograms — one obtained with a lateral projection and one with a postero-anterior, the latter angled 30° towards the feet — if it is assumed that the cross-section of the heart in a postero-anterior direction is an ellipse. In the anterior view, h_0 is the greatest diameter in the cranio-caudal direction and g_0 the distance between the tangents parallel to h_0 (Fig. 1).

If the measurements that would have been obtained with parallel rays are calculated, they will be h, g and d, if they are determined on the principles to be given in the following. This also applies if they are measured directly with the correction method described by LARSSON & KJELLBERG.

H is calculated from h, H being the distance between the lines parallel to d, which are tangents to the cross-section containing the diameter

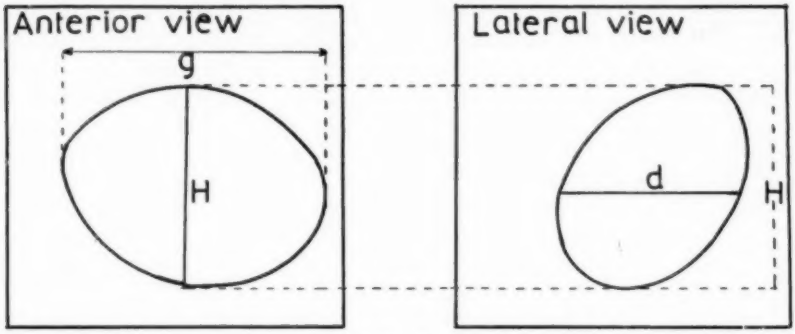


Fig. 2. Anterior and lateral views of the heart, using parallel rays perpendicular to the film.

d (see Figs. 1, 2). If H and d coincide with the main axes of the ellipse, we obtain

$$H = h\sqrt{1 - \frac{1}{3}\cdot\frac{d^2}{h^2}}$$

As KAHLSTORF pointed out, the angle formed by d with the large axis of the ellipse is immaterial from the point of view of the ellipsoid theory when the direction of the beam in the postero-anterior projection is parallel with d. When, however, the beam forms an angle with d, it is not immaterial. If this angle only varies slightly, it is nevertheless possible to calculate H from $\frac{d}{h}$.

Irrespective of the shape of the anterior view, the following assumptions may be made.

The relationship between the depth and the altitude of each sagittal section is constant and is equal to $\frac{d}{H}$. The surface of such a section is equal to the product of the altitude and the depth multiplied by a constant k. Let the variable y denote the diameter in a cranio-caudal direction from 0 to g, so that $y^2 = f(x)$. We then obtain

$$V = k \cdot \frac{d}{H} \int_0^g f(x)\, dx$$

If $y_1 \ldots y_i \ldots y_n$ are a series of diameters at equidistant intervals,

$$I = \int_0^g f(x)\, dx$$

can be estimated with a sufficient degree of accuracy by means of, for example, Simpson's rule.

We made such an estimation in 31 unselected cases, men and women between the age of 20 and 40. Use was made of 10—15 diameters at intervals of approximately one centimeter. The values found were in good agreement with those obtained on the hypothesis of the ellipsoid shape of the heart, according to which

$$I = \frac{2}{3} g H^2$$

The standard deviation for the difference between the values obtained with the different methods was approximately 3 per cent. The integrated values were somewhat lower, corresponding to 0.65 gH^2.

Because, according to the assumption of the elliptic shape of the sagittal section, the numerical value of k is $\frac{\pi}{4}$, the formula for the volume will be the same as for the ellipsoid, *i. e.*,

$$V = \frac{\pi}{6} gHd \text{ or}$$

$$V = F \cdot g\, h\, d$$

where

$$F = \frac{\pi}{6} \cdot \sqrt{1 - \frac{1}{3} \cdot \frac{d^2}{h^2}} \quad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

According to the ellipsoid hypothesis, l and b may be substituted for g and h according to the foregoing definitions.

If it is presumed that the foregoing assumptions regarding the general shape of the heart are relevant, it should be possible to calculate the cardiac volume as the product of three parameters and a factor, F, which in turn is a function of the quotient of two of the parameters, d and h.

It should be possible, by means of statistical testing, to verify whether F exists as a variable function of $\frac{d}{h}$ and whether it is of practical importance.

For this reason, a calculation was made on part 2 of the material of the regression equation between the product ghd as a dependent variable, and of the body weight and volume of the blood (according to Sjöstrand's method) as independent variables.

According to the forementioned hypothesis, the values for the product ghd corresponding to a low value for $\frac{d}{h}$ should show a one-sided

deviation between the values found and those calculated according to the regression equation. This also applies to cases with a high quotient.

The quotient of $\frac{d}{h}$ varied between 0.58 and 1.06. In the 11 cases in which $\frac{d}{h}$ was less than 0.70, 2 values were larger and 9 smaller than those calculated. The deviation amounted to 5 per cent of the mean for the whole series. On the other hand, the expected deviation from the cases with a high quotient was not found. In 10 cases this was more than 0.90. In 5 of them the values were larger and in 5 smaller than those calculated.

The investigation thus indicates that F varies with $\frac{d}{h}$, but rather analogously with the findings of LARSSON & KJELLBERG in hearts of cadavers than in accordance with the formula based on the ellipsoid hypothesis.

A corresponding test was made with the parameter system lbd. The product ghd was then exchanged for the product lbd and $\frac{d}{h}$ for $\frac{d^2}{lb}$. The result was in good agreement with the previous test. Of the 11 cases with the lowest quotient $\left(\frac{d^2}{lb} \text{ less than } 0.40\right)$ 10 showed a one-sided deviation, the volume found being less than that calculated.

The regression equation with respect to height, weight and pulse rate, was calculated on 63 persons from part 1 of the material. It did not however, reveal any definite tendency for the size of the deviation to be correlated to the quotient of $\frac{d^2}{lb}$.

The results of the study of the influence of angulation may be summarized as follows. It appears reasonable, from a theoretical point of view, for the cardiac volume to be calculated with the help of three parameters, it then being the product of the parameters and of a constant. In the case of »very flat» hearts $\left(\frac{d^2}{lb} \text{ less than } 0.4\right)$, it is possible that a correction must be made, in similarity with the findings of KJELLBERG & LARSSON on hearts of cadavers.

The values for the cardiac volume given in the present study are based on the conception of F as a constant. For practical reasons, it has been fixed at 1. If an approximate expression in milliliters is desired, the figures obtained with (1) are multiplied by 0.5, which corresponds to F for the typical value of $\frac{d}{h}$.

Magnification

BLASIUS (1938) showed that it is possible from a roentgenogram to make a sufficiently accurate calculation of the measurements had parallel rays been used. This was provided that the shape of the heart could be regarded as an ellipsoid. In the following, correction for the magnification denotes the calculation of the measurements that would have been obtained with parallel rays.

If the diameters measured — without correction for the magnification — are l_0, b_0 and d_0, and the diameters corrected for the magnification are l, b and d, and if the distance between the centre of the heart and the casette in the postero-anterior projection is v_1 and that in the lateral projection is v_2, and if the focal distance is f, the magnification is corrected according to the formula

$$lbd = M \cdot l_0 b_0 d_0$$

where

$$M = \left(\frac{f - v_1}{f}\right)^2 \cdot \frac{f - v_2}{f}$$

The magnification factor for a group of 62 persons from part 1 of the material varied between 0.69 and 0.76.

Whether anything was gained by using the correction was tested as follows.

A calculation of the product $l_0 b_0 d_0$ (uncorrected series) and of the product lbd (corrected series) was made for the forementioned group.

The linear regression for the body weight was calculated for both series. The standard deviation from the regression line was 10.4 per cent of the mean for $l_0 b_0 d_0$ in the uncorrected series and 9.7 per cent of the mean figure for lbd in the corrected series.

If the uncorrected figures are studied, it is found that the difference between the values calculated according to the regression equation and the products found are not the same for values with a high correction factor as for those with a low factor.

The magnification factor was greater than 0.71 in 13 cases and less than 0.74 in 13.

Nine out of the 13 cases with the lowest magnification factor had a larger product than that calculated with the regression equation. In the other group, 11 values were lower than the calculated ones. The difference between the means for the deviations in both groups was 11.5 per cent of the mean for the products for the whole series of 62 cases. The difference is probable ($0.02 > p > 0.01$).

Thus, allowance for the variation in the magnification appears to result in a not inappreciable increase in the accuracy of the predicted cardiac volumes.

Standard Error of the Single Determination

The variations in the cardiac volume due to the cardiac cycle, respiration and the position of the body, as well as the variations included in the standard error of a single determination, are dealt with in this section. One hundred and seventeen double determinations were made for this purpose.

The subjects to be examined were divided into five groups. Two determinations of the cardiac volume were made in each case. In each group, the first determination on each person forms a series (series 1 in the table). Similarly, series 2 is composed of the second determination in each of the cases.

In the first group, both determinations were made in the same way, with the subject in the prone position, the exposure being made during maximum diastole and slow superficial breathing, under control of ECG relay. In each of the other groups, a change was made in one of the forementioned conditions in one or both series. Reference is made to the table for further details regarding the composition of the respective groups.

Table

The Effect of Various Factors on the Standard Error of a Single Determination

Group	Method of Examination		No. of Cases		Δ	$S^2\Delta$	u
	Series 1	Series 2	Men	Women			
I	Standard method[1]	Standard method	27 18—53 yrs.		0.00132	0.00035006	3 %
II	Exposure during systole	Standard method	14 19—66 yrs.	10 29—47 yrs.	0.00154	0.00062071	4 %
III	Standard method	Exposure after deep inspiration	18 16—64 yrs.	7 16—54 yrs.	0.00012	0.00064060	4 %
IV	Standard method	Upright position	24 19—20 yrs.			0.00036366	3 %[2]
V	Exposure without ECG relay	Exposure without ECG relay	15 19—77 yrs.	2 18—76 yrs.	0.02061	0.00053189	4 %

[1] Standard method denotes examination in the prone position during maximum diastole and superficial respiration.

[2] The effect of the variation caused by the pulse rate is eliminated.

In order to avoid subjective influences in the measurement of the roentgenograms, the same precautions were observed as those in a similar investigation made by AXÉN, LINDGREN & MALMSTRÖM (1946).

As a rule, two examiners each measured the parameters in half of each series in each group. Thus, the measurements for each person were made only once by the same examiner. In one group (II) both measure-

ments were made by the same examiner at an interval of one week. In another group (V) two examiners each measured one series.

In group I, the difference between the figures obtained for the volume in the two determinations was plotted against their mean. A tendency to a correlation was found, the difference increasing with an increase in the mean. It therefore appeared most suitable to use the logarithms of the volume for the statistical analysis.

The following symbols were used:

$$V_1 = \text{the volume in determination I}$$
$$V_2 = \text{» » » » II}$$
$$x_1 = {}^{10}\log V_1$$
$$x_2 = {}^{10}\log V_2$$
$$\triangle = x_1 - x_2$$
$$\bar{\triangle} = \frac{1}{n} \Sigma(\triangle)$$
$$S^2_{\triangle} = \frac{1}{n-1} \Sigma(\triangle - \bar{\triangle})^2$$
$$s_{\bar{\triangle}} = \frac{s_{\triangle}}{\sqrt{2}}$$

If the antilogarithm is calculated, we obtain

$10^{\pm s} \sim 1 \pm u$, where u is the standard error as a percentage of the mean.

Results. In the first group, the roentgenograms were made in the same way in both series, *i. e.*, with the subject in the prone position with exposure under ECG control during maximum diastole and superficial respiration. The value obtained for u was 3 per cent, which is thus an estimation of the standard error of a single determination.

In the second group (II), the procedure was the same as in group I, except that the first series was taken during systole and the second during diastole.

The time for the exposure and its length were recorded synchronously with the ECG, thus ensuring that the exposure was made at the right phase of the cardiac cycle. The pulse rate on exposure was also noted from the ECG.

No statistically significant difference between the cardiac volume during systole and diastole could be noted for the whole material in this group. In 11 cases the pulse rate was below 70. In 9 of them the volume during systole was smaller than during diastole ($\bar{\triangle} = -0.01056$, $s_{\bar{\triangle}} = 0.02190$. $0.1 < p < 0.2$). The difference is of the nature that could

be expected but is not statistically probable in this small series. In the remaining 10 cases, with a pulse rate over 70, the mean volume was larger during systole than during diastole. In these cases as well, the difference was not probable.

The investigation indicates that the effect of the cardiac cycle on the cardiac volume is inappreciable. A possible exception is in the case of persons with a low pulse rate. If, in addition, the very slight probability of the exposure being made during systole is taken into consideration, it should be a very rare occurrence for the cardiac volume to be incorrectly estimated when exposure is made irrespective of the phase of the cardiac cycle. This is an agreement with the statements made earlier by JONSELL.

In the third group (III) the investigation was in accordance with that in group I, except that in the second series exposure was made while the subject held his breath after deep inspiration. No statistical difference was found between the two series. Thus, no support was afforded to the assumption that exposure during inspiration shows a smaller cardiac volume. It is conceivable that the increase in the intrathoracic pressure during inspiration only takes effect after a lapse of time. The following additional test was therefore made. Roentgenograms were taken of four healthy, 20 year old men, 15, 30 and 45 seconds respectively after holding their breath during deep inspiration. No difference was found in the cardiac volume after the respective intervals.

The investigation in the fourth group (IV) was made in the same way as in group I, except that in the second series the patients were in the upright position. The pulse rate on exposure was noted from the ECG. The mean cardiac volume in the upright position was 92 per cent of that in the prone position. The difference between the figures for the cardiac volume showed a significant correlation to the pulse rate ($r = -0.70$). When the variation due to the pulse rate was eliminated, the remaining variation was approximately of the same order of magnitude as the standard error of a single determination in group I.

Finally, in the fifth group (V) both series were taken as in group I, with the exception that the exposure was made irrespective of the phase of the cardiac cycle, *i. e.*, without ECG relay. As was anticipated, the variation was not markedly greater than in group I. The difference, $\bar{\Delta}$, probably exceeds 0. This is presumably due to the fact that the measurements in the two series were made by different examiners.

Final results. The results are assembled in the Table. In group IV, s^2_{Δ} denotes the remaining variance after elimination of that dependent on the pulse rate when the subject is standing. If the sums of squares within groups are totalled for the entire material, u is obtained with 111 degrees of freedom. The value of u is then 3.7 per cent.

The 5 per cent confidence interval is 3.2—4.1 per cent.

If the figure of 3.3 per cent given in AXÉN, LINDGREN & MALMSTRÖM's study of the cardiac volume in the upright position according to the method of LILJESTRAND, LYSHOLM, NYLIN & ZACKRISSON is compared with the results of similar calculations in the present study, it is found to correspond to the standard error of the mean in a double determination. If the standard error of a single determination is calculated from the published figures with the formula

$$s_x = \sqrt{\frac{\Sigma(V_{i_1} - V_{i_2})^2}{2(n-1)}}$$

where s_x is the standard error of a single determination in milliliters and n the number of differences, $(V_{i_1} - V_{i_2})$, the standard error of a single determination corresponds to the value 37 ml, with the confidence limits 30—52 ml on the 5 per cent level.

If the standard error of a single determination is expressed as a percentage of the mean, 809 ml, the figure will be 4.6 per cent (3.7 — 6.4 per cent).

To sum up, the following statements may be made:

1. The standard error of a single determination in an examination in the prone position is relatively slight, presumably less than that in the upright position according to LILJESTRAND, LYSHOLM, NYLIN & ZACKRISSON's method. It is, however, difficult to decide whether the latter statement is correct, since the figures published do not permit a statistical comparison.

2. An increase in the error may be anticipated in persons with a low pulse rate, unless the exposure is made at the right phase of the cardiac cycle.

3. No increase in the error can be demonstrated if exposure is made on deep inspiration. Especially in fat individuals the heart contours may, however, be better visualized if exposure is made in deep inspiration.

4. On examination in the upright position with 30° angulation of the tube, it is probable that there is no appreciable increase in the standard error of a single determination or in the variation between different individuals, if allowance is made for the pulse rate.

The following may be of interest from a practical point of view. We can assume that we have two successive determinations made on the same person and that we wish to ascertain whether the difference in the figures for the volume is greater than that permitted as a random deviation. With the use of the upper confidence limit for $s_\triangle$ on the 5 per cent level, and assuming that the distribution of $\triangle$ is approximately

normal, it may be calculated that the difference is less than 12 per cent in 95 cases out of 100.

The Relationship of the Cardiac Volume to the Height, Weight and Pulse Rate

It has been shown that the cardiac volume of adults in the upright position is correlated to the body weight. It has also been correlated to the surface area of the body, calculated from the height and weight (according to DUBOIS) taking into consideration sex and age (LILJESTRAND et al. 1939).

LUDWIG (1939) found, on simultaneous testing of a number of characteristics, that the heart volume in the upright position had a statistically significant partial correlation not only to the body weight but also to the breadth and depth of the thorax. The height had a negative correlation coefficient. This implied — amongst other things — that tall (thin) persons have a smaller heart than short (fat) ones. The partial correlation coefficient was not, however, significant.

LUDWIG calculated the cardiac volume from the three characteristics: body weight, breadth and depth of the thorax in a series of 120 young men. He found a standard deviation from the regression equation (11 per cent) which was 1 per cent lower than if the cardiac volume was calculated from the body weight alone.

KJELLBERG, RUDHE & SJÖSTRAND (1949) demonstrated that the cardiac volume may be calculated from the total haemoglobin of the body. The method is therefore also suitable for persons with a high physical working capacity.

It also appeared of interest to determine whether any correlation could be found between the cardiac volume and the pulse rate in the prone position.

The first series — *i. e.*, the same as that mentioned earlier in connexion with testing of the factor — consisted of 63 army volunteers, about 20 years of age. The pulse rate was determined in the prone position in connexion with the determination of the cardiac volume, without resting before it.

The partial regression equation was calculated with the method of least squares. Thus:

$Y = b_1W + b_2L + b_3P + C$, where Y denotes the cardiac volume expressed as the product lbd, W the body weight in kilograms, L the height in centimeters, P the pulse rate in the prone position and C is a constant.

The best estimates were with the use of the confidence limits at the 5 per cent level:

$$b_1 = 22.7 \pm 6.00$$
$$b_2 = -4.39 \pm 6.20$$
$$b_3 = 3.37 \pm 3.13$$
$$C = 950$$

The coefficient for weight had the highest degree of significance ($p < 0.001$ for the hypothesis that it does not differ from 0). The coefficient for the pulse rate had a lower degree of significance ($p < 0.05$), whereas the coefficient for the height was not significant. It was, however, negative, as LUDWIG found. It is therefore possible to conclude that the height has some influence — even though inappreciable — on the cardiac volume.

The standard deviation from the volume calculated from the regression equation was 115 (58 ml) $\pm$ 21 (11 ml) at the 5 per cent confidence level. This corresponds to 7.8 per cent of the mean for the volumes.

If the cardiac volume is calculated only with regard to body weight, the corresponding deviation will be 119. With the regression equation $Y = b \cdot W + C$, the estimate is $b = 20.8$, $c = 74$.

The decrease in the standard deviation is mainly dependent on the body weight. Only an inappreciable increase in the accuracy of the predicted values is obtained by taking into consideration the pulse rate and the height.

The regression equation of the cardiac volume with respect to the body weight and the pulse rate was calculated on another series of 41 persons of the same age. The pulse rate was then recorded in the prone position after resting for 30 minutes. Its coefficient differed significantly from 0. ($t = -3.72$) $p < 0.01$.

If the regression equation is written as $Y = b_1W + b_2P + C$ the estimates would be

$$b_1 = 15.1$$
$$b_2 = -9.87$$
$$C = 1{,}070$$

When the regression equation thus obtained was applied to 8 well-trained athletes, they were found to have a considerably larger cardiac volume than that anticipated from the regression equation. This must be interpreted as an indication that the two linear characteristics — *i. e.*, body weight and pulse rate — are insufficient for a determination of the cardiac volume and that other factors must also have an effect.

In investigations made in the U. S. A. in particular, the anterior surface of the heart alone has been used as a measure of the size of the heart, the subject being in the upright position. It therefore appeared of interest to ascertain whether the use of the anterior surface of the

heart with the subject in the prone position (according to our technique) would result in as good a correlation to the other characteristics as the cardiac volume.

The surface ($A = lb$) was therefore substituted for the volume in the regression equation for the series of 63 army volunteers.

It was found that the multiple correlation coefficient between Y and L, W, P was 0.71 and that between A and L, W, P 0.61.

If the value for the volume was used, the original variance was reduced by approximately 50 per cent. If the surface was used, it was reduced by approximately 30 per cent.

The volume therefore appears to be a considerably better expression of the size of the heart than the surface of the anterior view.

SUMMARY

The first section deals with the method for determination of the cardiac volume with the subject in the prone position. The effect of magnification and of oblique projection and, as far as possible, of individual variations in the position and shape of the heart are discussed from the theoretical aspect and tested in statistical series.

The second section comprises an estimation of the standard error of a single determination and of the effect of various factors upon it.

The last section deals with the relationship of the cardiac volume to the height, body weight and pulse rate.

ZUSAMMENFASSUNG

Der erste Abschnitt behandelt die Methoden für die Berechnung des Herzvolumens bei der Untersuchung in liegender Stellung. Es wird der Einfluss der Vergrösserung und Schrägprojektion und soweit wie möglich die individuellen Abweichungen der Lage und Form des Herzens vom theoretischen Standpunkt aus besprochen und in statistischen Reihen nachgeprüft.

Der andere Abschnitt befasst sich mit einer Schätzung des methodischen Fehlers und mit dem Einfluss verschiedener Faktoren auf diesen.

Der letzte Abschnitt behandelt die Beziehung zwischen Herz-Volumen und Körper-Länge, Körper-Gewicht und Puls-Frequenz.

RÉSUMÉ

La première partie concerne la méthode par laquelle on peut calculer le volume du coeur en position couchée. L'influence de l'agrandissement, de la projection oblique et, dans la mesure du possible, des différences individuelles dans la position et dans la forme du coeur est discutée du point de vue théorique et recherchée par des séries statistiques.

La deuxième partie contient une évaluation de l'erreur de la méthode et de l'influence des divers facteurs sur celle-ci.

La troisième partie concerne les rapports existant entre le volume cardiaque d'une part et la taille, le poids du corps et la fréquence du pouls d'autre part.

REFERENCES

Axén, Lindgren, Malmström: Nord. Med. 29 (1946), 592.
Blasius: Fschr. Röntgenstr. 57 (1938), 567.
Cramér: Sannolikhetskalkylen och några av dess användningar. Upsala 1949.
Fisher: Statistical Methods for Research Workers. Edinburgh. Tenth Edition 1948.
Jonsell: Acta radiol. 20 (1939), 325.
Kahlstorf: Fschr. Röntgenstr. 45 (1932), 123.
Kjellberg, Rudhe, Sjöstrand: Acta radiol. 31 (1949), 113.
Larsson, Kjellberg: Acta radiol. 29 (1948), 159.
Liljestrand, Lysholm, Nylin, Zackrisson: Am. Heart J. 17 (1939), 406.
Ludwig: Fschr. Röntgenstr. 59 (1939), 1.
Sjöstrand: Acta physiol. Scandinav. 16 (1948), 211.

FROM KING GUSTAF V JUBILEE CLINIC IN LUND, SWEDEN
(DIRECTOR: BERTIL EBENIUS)

ROENTGEN ROTATION THERAPY IN CANCER OF THE ESOPHAGUS[1]

Dosage problems. Preliminary results

by

Inge Gynning

The theoretical aspects of rotation therapy have attracted the interest of radiologists ever since the beginning of the twentieth century. Reports based upon clinical experiences, on the other hand, have been very sparse and have not appeared until the latter part of the third decade and, more particularly, until after 1940. Most of these reports have concerned carcinoma of the esophagus, which lends itself best to this form of treatment. Roentgen therapy with the rotation method involves crossfire irradiation with a maximal utilization of the multiple field principle. The roentgen tube may describe a partial or full circle around the patient or the patient may rotate around an imaginary axis through the tumor while the roentgen tube remains stationary. At the Jubilee Clinic in Lund the latter technique has been used. The apparatus was procured by Professor LARS EDLING in 1942 and since then it has been improved by several technical devices which facilitate the execution of the treatment and enable a more exact determination of the tumor dose.

Technique

Fig. 1 shows the present technical arrangements. The patient is placed in a revolving chair with the arms upstretched and the hands resting on a trapeze. He is fixed by means of a band around the upper part of the thorax and another around the legs below the knees. The roentgen tube and the fluorescent screen are movable in a vertical direc-

[1] Submitted for publication, Dec. 8, 1950.

tion. The distance between the focus and the rotation center is 53 cm and between the focus and the fluorescent screen is 106 cm. $^1/_2$ mm Cu + 1 mm Al filtration is used with 170 kV., 15 mA., and a half-value layer of 0.85 mm Cu. The intensity in the region of the tumor is 10 to 15 r per minute. Continuous fluoroscopic control is carried out from adjacent observation cabine from which the diaphragm is also manipulated.

Fig. 2 shows the fluorescent screen provided with adjustable rubber bands which mark the limits of the field and its vertical and horizontal middle planes. This arrangement makes it possible to keep the size of the field constant in each treatment and facilitates the control of the position of the tumor in the field of treatment.

Fig. 1.

Scandinavian radiologists have been particularly interested in roentgen rotation therapy. Lars Edling (2), Jens Nielsen et al. (17, 18, 19), Howard Nielsen (14, 15, 16), Carl Krebs et al. (16) and others have given detailed reports on the theoretical problems as well as on the essential advantages of this method over roentgen therapy with stationary fields. This paper is confined to three important practical problems which arise in the rotation treatment of intrathoracic carcinoma of the esophagus and which are closely interdependent: 1. The determination of the tumor dose. 2. The magnitude of the daily tumor dose. 3. The magnitude of the total tumor dose.

Dose Measurements

1. *The determination of the tumor dose* must be as exact as possible because, among other reasons, the total dose must generally be so high

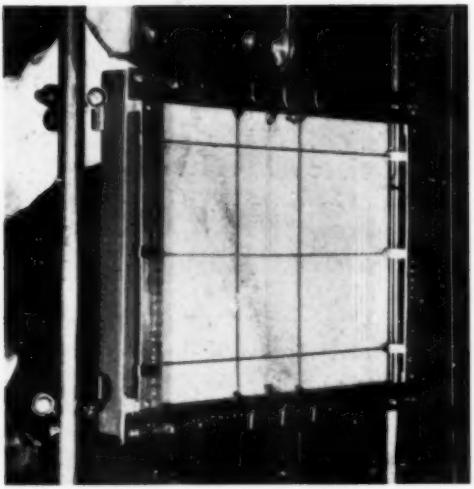


Fig. 2.

that it approaches the tolerance dose of normal tissue. The mathematical calculation of the tumor dose according to formulas published by MESNIL DE ROCHEMONT (3, 4) has very little practical significance as it does not exclude certain sources of errors such as different thoracic densities in patients with the same thorax measurements. NIELSEN and his coworkers have reported comparative measurements on phantoms, where the relation between skin dose and tumor dose could be determined within certain limits. NIELSEN (19) points out, however, that *the only way in which the tumor dose can be determined with any accuracy is by direct measurement in the esophagus.* EDLING made the same statement as early as 1943 and in our clinic the tumor dose in the esophagus was in all cases measured with Sievert's ionization chambers. Since 1944 specially constructed rubber bougies with aluminium containers holding two ionization chambers and indicators have been used (LIDÉN (3)). The construction of the bougies is shown in fig. 3. To the left is a roentgenogram of the aluminium container with lead indicators. Fig. 4 shows a roentgenogram of the bougie in the esophagus. The two chambers are situated between the two indicators.

The introduction of the bougie is usually easy. The pharynx may be anesthetized but this is usually unnecessary. If there be considerable mucus present the patient may receive preliminary treatment with atropine. We endeavour to place the chambers in the center of the field; in the case of marked constriction which cannot be passed without resistance we have to be satisfied with a less ideal position. An approximative determination of the tumor dose is obtained in such cases. A prerequisite is, however, that the upper chamber be situated at least 1 cm below the upper limit of the field and that there be comparatively good uniformity between the two chambers. At a later stage in the treatment, when the bougie, as a rule, passes the constriction more easily, reliable values may be obtained. A persistent stricture in a few cases necessitated esophagoscopy for the introduction of the bougie.

In order to obtain a more exact determination of the tumor dose,

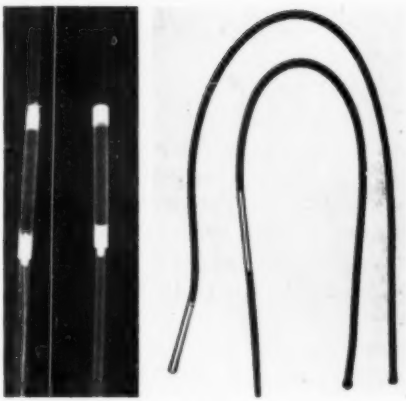


Fig. 3.

Fig. 4.

we have improved these measurements during the last year by employing a sound, containing eight ionization chambers in a row with a lead indicator in the middle. With such an arrangement one gets a better idea of the dose distribution within the field of treatment and in its immediate vicinity. These dose differences may be considerable even within the tumor area. The doses mentioned in this paper are usually measured in the center of the field and represent therefore in most cases the maximum values in the tumor area. Nothing can be said of the minimum value.

In a few cases the patients developed a slight rise in temperature in connection with the chamber measurement and, exceptionally, high temperatures and rigours; penicillin was administered in these cases and often given prophylactically in subsequent measurements. In no case did any serious complication occur.

The number of measurements depended on the uniformity of the values obtained. When there was near-agreement, 4 to 5 measurements were considered sufficient.

If such a small number of measurements are to form the basis for the calculation of the total tumor dose after more than 30 treatments, all factors affecting the size of the dose must be kept constant. The tumor

area, for example, must be carefully centered in each treatment. *The patient should, therefore, be well immobilized and the fluoroscopic control must be carried out by a radiologist.* The size of the field must be the same in all treatments.

It is also desirable that the intensity of the emanating primary beam is controlled daily. We have further tried to obtain a secondary control of the tumor dose in each radiation by measuring the penetration of the radiation in the center of the field. These experiments are still in the preliminary stage.

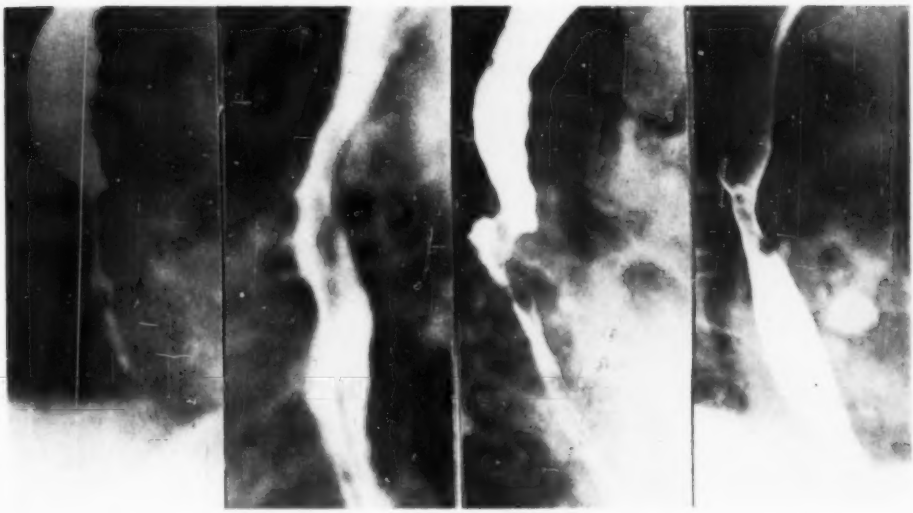
Daily Dose

2. Opinions vary as regards *the most suitable magnitude of the daily tumor dose.* BÜTIKOFER (1) has given only 100 r daily which we consider inadequate, for it probably allows too great a recovery of the cells of the tumor. NAKAIDZUMI and MIYAKAWA (12) have given doses of 250 to 500 r which, on the other hand, according to our experience, are too high. It is true that doses up to 300 r can sometimes be tolerated, but the risks of perforation into the surrounding organs increase with too rapid a disintegration of the tumor. In addition, the general condition of the patient is affected. NIELSEN (19) has given 100 to 200 r, usually 150 to 200 daily in two sittings. This dose is almost the same as ours, 200 to 225 r, and fulfils, we have found, the demand of being as high as possible without causing too great a general or local reaction; it is suitable as regards the time factor.

Total Dose

3. *The total tumor dose* given by NAKAIDZUMI and MIYAKAWA (12) in 5 cases has exceeded 10,000 r. These patients all succumbed within a short time to complications from overdosage. One group received between 7,000 and 10,000 r and another less than 5,000 r, during a period of 10 to 30 days. No data are submitted as to the results. NIELSEN (19) and BÜTIKOFER (1) have given approximately 5,000 r, the former usually for 35 to 42 days.

At the Jubilee Clinic in Lund 5,000 r was originally given during a period of 25 to 30 days. Since the majority of these patients died with local recurrences within one year, the dose was gradually increased, first to 6,000 and afterwards to 6,500 r per 35 to 40 days. Recurrences still occurred and the dose in 4 cases was increased to approximately 7,000 to 7,200 r per 35 to 40 days. Three of these patients died within three to five months due to overdosage complications and about one month after the completion of the treatment the fourth patient developed an ulceration in the tumor area. Gastrostomy was performed but the fistula



a. b. c. d.

Fig. 5. Case 9, table 2. a. before treatment b. immediately after treatment c. 1 month later, large ulcer, gastrostomy performed d. 4 months later, healed after gastrostomy.

closed 4 months later and when the patient was roentgenologically healed he showed no clinical signs. He lived free of signs for 2 years following the treatment but later died from cardiac disease (no. 9, table 2). See fig. 5.

On the basis of these cases we concluded that the tolerance dose of the tissues probably lies around 7,000 r per 35 to 40 days.

During the last few years, therefore, we have given between 6,500 r per 35 and 6,800 r per 40 days. The influence of the time factor has been evaluated according to Strandqvist's diagram of fractionation for roentgen treatment of carcinoma of the skin (20). (Fig. 6.) Unfortunately, complications due to overdosage must be expected when doses of this magnitude are administered, *particularly if the determination of the tumor dose is not sufficiently exact*. For this reason, probably, we had 8 additional cases of different kinds of overdosage complications.

Even though carcinoma of the esophagus is fairly often histopathologically comparatively undifferentiated, and is relatively radiosensitive, there are in this respect considerable variations. A few carcinomas are so sensitive to radiation that regression, both clinically and roentgenologically, can be demonstrated at an early stage of the treatment. This

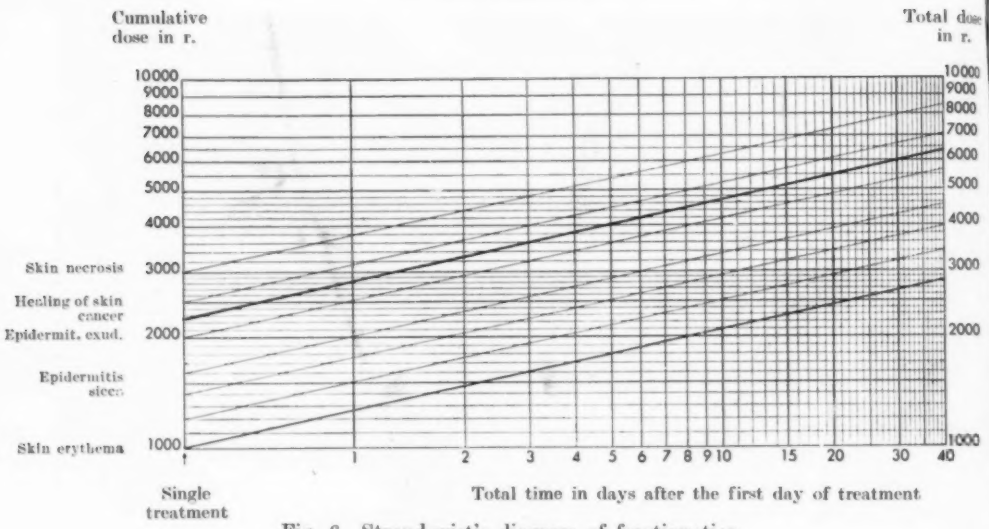
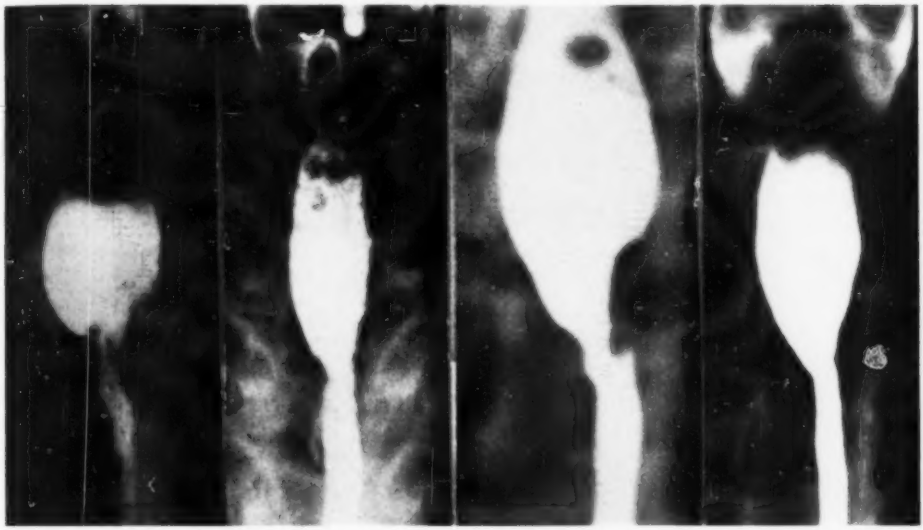


Fig. 6. Strandqvist's diagram of fractionation.

fact explains, no doubt, the good results obtained in cases where a comparatively low tumor dose has been given. NIELSEN (19), for instance, mentions that 3 patients were free of signs for more than 2 years following a calculated total tumor dose of 4,200 to 4,300 r per 18 to 24 days. We have one similar case (no. 8, table 2) which is worth mentioning. In September, 1940, a 66-year-old man received roentgen treatment with fixed fields, approximately 4,600 r during 26 days, for a carcinoma situated in the upper part of the esophagus. After almost 6 years without signs he returned for a follow-up examination without clinical signs, but with a roentgenologically and later also microscopically verified local recurrence. Rotation treatment was given in July, 1946 (4,000 r/26 days). He had no signs 2 years after the last treatment and more than 8 years after the first one. He developed a new local recurrence about $2^1/_2$ years after the last treatment (fig. 7). It should be pointed out, however, that the tumor only involved a portion of the esophagus 1 to 2 cm long, a fact that probably contributed to the temporary healing after such a low total tumor dose. The distribution of the dose will naturally be more even and more satisfactory in a smaller than in a more extended field of treatment where the difference between the central and the peripheral dose may be considerable. When the tumor involves greater portions of the esophagus, overdosage may occur in the center and underdosage in the periphery.

The highly radiosensitive early cases are rare, however, and ac-



a. b. c. d.

Fig. 7. Case 8, table 2. a. before treatment 1940
b. after treatment (stationary fields)
c. recurrence 1946
d. symptomfree after rotation therapy.

cording to our experience with our present technical capabilities the maximum tumor dose given must usually be high and lie somewhat below the tolerance limit of the tissues, if better results are to be obtained throughout. The maximum tumor dose should thus approach but not exceed 6,500 r per 35 days or 6,800 r per 40 days.

Results

In support of the dosage suggested above a preliminary report of our results will be given. The present series of cases was treated during a four-year period, from October 1, 1943 to October 1, 1947; the minimum time of observation (up to October 1, 1950) is three years.

The cases treated before October 1, 1943, are not included as the total tumor dose then given was completely inadequate and could not always be determined with sufficient accuracy.

The material from this four-year period comprises all patients with carcinoma of the esophagus, whom on admittance showed no obvious clinical peripheral metastases nor any involvement of the cardia.

On evaluation of the results of the treatment one should take into

a. b.

Fig. 8. Case 1, table 2. a. before treatment
b. living 6½ years after treatment.

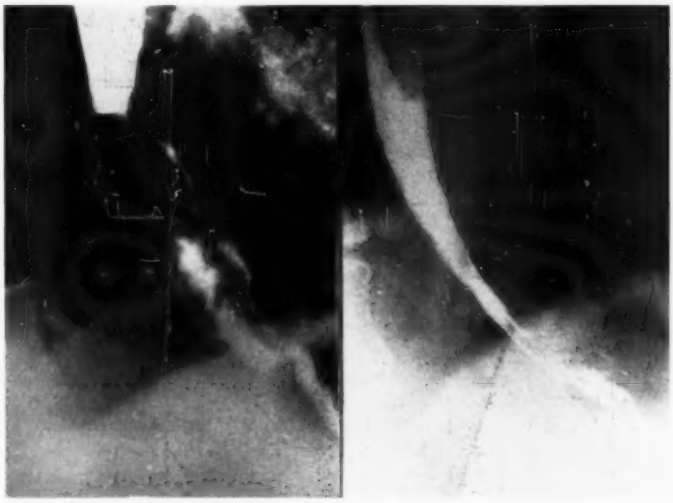
consideration the continuous development of therapeutic technique and the variation of the dosage within wide limits. There are thus several cases in our material in which according to our present view, overdosage or underdosage has been administered. All patients were accepted for treatment irrespective of age, tumor size, or general condition.

The series includes 88 patients, 54 men and 34 women.

The average age was 67 years at onset of treatment.

In three cases no microscopic diagnosis for some reason or another could be obtained. The roentgenological diagnosis in these cases was unmistakable, however. Two died comparatively soon after the completion of the treatment. All the other cases were verified microscopically.

Eight patients died during the course of treatment. At autopsy they all had very advanced carcinomas with infiltration into adjacent organs and abundant mediastinal and peripheral metastases.



a. b.

Fig. 9. Case 2, table 2. a. before treatment
b. after treatment. Died from intercurrent disease after 5½ years.

Table 1

Group	I < 6,000 r/ 35 days	II 6,000–6,400 r 35 days	III > 6,400 r/ 35 days
No. of cases	12	26	39
Died within 1 year	8	20	24
Living after 1 year with recurrence or metastases	3	3	4
1 year cure	1	3	11
2 — » —	1	2	7
3 — » —	—	2	6
4 — » —	—	2	3
5 — » —	—	2	2
6 — » —	—	1	—
Probable local recurrence	12	20	20
No local signs of cancer: Alive and symptomfree 1/10 1950	—	1	4
No local signs of cancer: Died from intercurrent disease	—	2	5
No local signs of cancer: Died from overdosage-complications	—	1	5
No local signs of cancer: Died from metastases	—	2	5
No. of cases	12	26	39

Dose measured in the center of the tumor.

Table 2

Results of treatment up to 1st October 1950

No.	Sex	Age	Length of tumor	Location of tumor	Daily tumor dose r/min.	Total tumor dose r/days	Corresponding tumor dose/35 days[1]	Period of observation without local recurrence		Stricture	Remarks
								Years	Months		
1	♀	62	7.5 cm	middle	210/15	6,100/36	6,100/35	6	8	0	Living.
2	♂	79	5 »	lower	230/18	6,000/32	6,100	5	6	0	Died at age 85. No local recurrence. (No autopsy.)
3	♂	70	8 »	middle	275/15	6,600/28	6,900	5	4	Moderate	Living.
4	♀	68	10 »	middle	215/18	6,550/36	6,500	5	2	Total	Gastric fistula. Living.
5	♂	68	7 »	upper	250/25	6,500/36	6,500	3	1	0	Died from metastases of supraclavicular region and lungs. No local recurrence. (Autopsy.)
6	♀	59	6 »	middle	250/20	6,500/35	6,500	4	10	Marked	Living.
7	♂	68	5 »	lower	235/18	6,500/35	6,500	3	5	0	Probably died from cardiac disease. (No autopsy.)
8	♂	66	1 »	upper	190/19	4,000/26	4,800	2	4	0	Recurrence after approximately 2 years 6 months.
9	♂	75	5 »	middle	210/20	7,100/43	6,500	2	2	0	Died from cardiac disease. (Autopsy.)[2]
10	♂	62	4 »	middle	204/14	6,700/39	6,500	3	4	Marked	Rotated 240°.[3] Living.

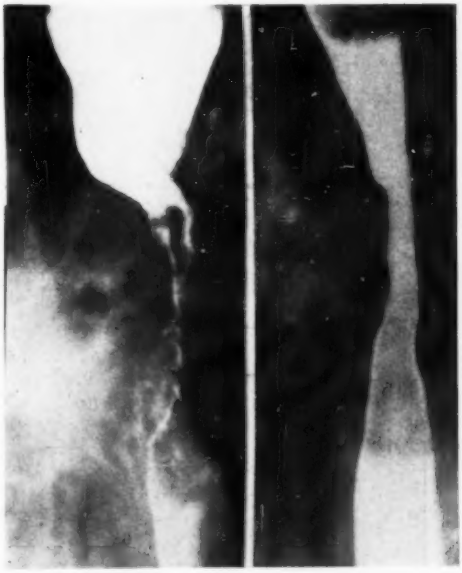
[1] According to Strandqvist's diagram of fractionation 20 (fig. 6).
[2] Radiation ulcer. Healed after gastrostomy.

In three cases the treatment had to be discontinued on account of the debilitated condition of the patient.

The treatment was carried through according to plan in 77 cases.

Distinct improvement was noted in 70 cases but only 50 were recorded as completely free of signs. Fifteen of the remaining 27 cases had roentgenological changes indicative of a persistent tumor. Signs of overdosage were seen in 12 cases, mostly in the form of ulceration in the esophagus within the tumor area. Two of these cases healed after gastrostomies which were later closed. In 4 of the remaining cases of overdosage autopsies revealed no signs of a growth within the irradiated area. The calculated maximum total dose in the 12 cases of complications due to overdosage was between 6,450 r and 7,050 r per 35 days but the actual dose was possibly higher.

In order to evaluate the results in relationship to the total tumor dose given during a certain period, the material is divided into three groups on the basis of Strandqvist's diagram of fractionation for radiation therapy of carcinoma of the skin (20) (fig. 6). Group II represents cases corresponding to the mean value of the healing dose $\pm$ 200 r, and group I and III cases in which the dose is lower and higher, respectively. It appears from table 1 that the number of patients who were cured for 1 year or more, is comparatively larger in group III than in groups I and II. The difference is particularly evident in those cases where no local recurrences appeared during the time of observation. These facts support the view that most carcinomas of the esophagus require a tumor dose of the magnitude mentioned above if healing is to be attained.



a. b.

Fig. 10. Case 3, table 2.
a. before treatment
b. living more than 5 years after treatment.

The 10 cases of at least 2 years' cure are of particular interest (see table 2). The frequent occurrence of strictures may be due to the high dosage, though other factors may also be important.

Fig. 8—11 show roentgenograms from some of the cases mentioned in table 2.

The therapeutic results from a numerical point of view are perhaps not particularly good, but considering the nature of the material: the high average age, mostly advanced cases, and, perhaps more important, an imperfect technique and dose control in the tumor area, the results are encouraging, particularly since a good palliative effect was obtained in a high per cent of cases. The patients tolerated the treatment well in spite of old age and comparatively poor general condition. The method is of special value in inoperable cases of carcinoma of the eosophagus regardless of location. When wider experience has been obtained it is possible that in so-called operable cases where the tumor is localized to the middle and upper third of the intrathoracic esophagus, equally

a. b. c.

Fig. 11. Case 5, table 2. a. before treatment
b. 3 years after treatment. No local recurrence. Died from metastases. Autopsy.

satisfactory or better results than with surgical intervention will also be obtained. Tumors situated in the lower third will probably still be better suited for surgical treatment than for radiological therapy on account of the anatomical conditions and the location of the regional lymph nodes.

SUMMARY

A short report is given on the therapeutic technique used in the Jubilee Clinic in Lund, Sweden, in roentgen rotation treatment of intrathoracic carcinoma of the esophagus. The determination of the focal dose as well as its daily and total magnitude are discussed. It is pointed out that the dose should be measured directly in the esophagus. The daily dose suggested is about 200 r and the total maximum dose about 6,500 r per 35 days or 6,800 r per 40 days.

Eighty-eight cases treated during a four-year period, 1943—1947, with a period of observation of at least three years, together with special consideration of the tumor dose administered, are reported.

Of the total treated (88) eight patients have been free of signs for at least 3 years (one for 6 years and four for 5 years).

ZUSAMMENFASSUNG

Ein kurzer Bericht über die in der Jubiläumsklinik in Lund, Schweden, bei der Röntgen-Rotations-Bestrahlung des intrathorakalen Oesophagus-Carcinoms verwandte Bestrahlungstechnik. Die Herddosis, die Tagesdosis und die Gesamtdosis werden besprochen. Es wird betont, dass die Messung der Dosis in der Speiseröhre selbst vorgenommen werden muss. Die vorgeschlagene Tagesdosis beträgt ungefähr 200 r und die gesamte Maximaldosis etwa 6,500 r in 35 Tagen oder 6,800 r in 40 Tagen.

Während der 4-Jahresperiode 1943—47 wurden 88 Fälle mit einer Beobachtungszeit von mindestens 3 Jahren behandelt, über die, unter besonderer Berücksichtigung der verabfolgten Tumordosis, berichtet wird.

Von allen Behandelten (88) waren 8 Patienten mindestens 3 Jahre lang symptomfrei (1 Patient 6 Jahre und 4 Patienten 5 Jahre lang).

RÉSUMÉ

Une courte relation de la technique de la thérapie rotative aux rayons roentgen appliquée dans le traitement des cancers intra-thoraciques de l'oesophage à la Clinique du Jubilé à Lund en Suède. La détermination de la dose focale ainsi que de la dose journalière et totale est discutée. Il est indiqué que la dose devrait être mesuré sur place dans l'oesophage. La dose journalière proposée est de 200 r et la dose maximum totale de 6,500 r pour 35 jours ou de 6,800 r pour 40 jours.

Quatrevingt-huit cas sont relatés. Ils ont été traités durant la période de quatre années de 1943 à 1947 et suivis pendant au moins trois ans. Les doses »tumeur» administrées sont également considérées.

Sur le total de ces cas (88) huit malades sont sans symptômes depuis 3 ans au moins (un depuis 6 ans et quatre depuis 5 ans).

BIBLIOGRAPHY

1. Bütikofer, R.: Die Rotationsbestrahlung des Oesophaguskarzinoms. Radiologia Clinica 16 (1947), 7.
2. Edling, L.: Experiences with roentgen rotation therapy. Acta radiol. 25 (1944), 427.
3. Lidén, K.: Depth dose measurements in the esophagus in roentgen rotation therapy. Acta radiol. 30 (1948), 64.
4. du Mesnil de Rochemont, R.: Die Dosierungsgrundlagen der Rotationsbestrahlung. Strahlenther. 60 (1937), 648.
5. — Zur Dosenberechnung bei der Rotationsbestrahlung. Strahlenther. 66 (1939), 593.
6. — Die Dosenverteilung bei der Rotationsbestrahlung. Strahlenther. 68 (1940), 221.
7. — Die Dosenverteilung bei der Rotationsbestrahlung. Über die Beeinflussung der Oberflächendosis durch den Streustrahlenmantel und durch die Unregelmässigkeit der Intensität im Strahlenkegelquerschnitt. Strahlenther. 69 (1941), 407.
8. — Die Stellung der Bestrahlungsverfahren mit wanderndem Strahlenkegel im Rahmen der modernen Entwicklung der strahlentherapeutischen Methodik. Strahlenther. 71 (1942), 512.
9. — Die Dosenverteilung bei der Rotationsbestrahlung. Der Wirkungsgrad der Rotationsbestrahlung mit auf einer Wendelbahn umlaufender Röhre. Strahlenther. 75 (1943), 121.

10. Nakaidzumi, M.: Eine neue Methode zur Konvergierung der Röntgenstrahlen (Konvergensbestrahlung). Strahlenther. 59 (1937), 168.
11. — und Adati, T.: Über Erfolge der Konvergensbestrahlung für Magenkarzinom. Strahlenther. 71 (1942), 343.
12. — und Miyakawa, T.: Über die räumliche Dosisverteilung der Röntgenstrahlen bei der Rotationsbestrahlung. Strahlenther. 66 (1939), 583.
13. — Zur Rotationsbestrahlung mit Hilfe einer ständigen Durchleuchtungskontrolle für den Oesophaguskrebs. Strahlenther. 68 (1940), 254.
14. Nielsen, H.: Determination of the dose in circular phantoms under rotatory irradiation. Acta radiol. 25 (1944), 183.
15. — Rotationsbestraaling. E. Munksgaard, Copenhagen 1948.
16. — Krebs, C. and Andersen, Poul E.: Rotation treatment of cancer of the esophagus. Acta radiol. 32 (1949), 304.
17. Nielsen, J. and Jensen, H.: Some experimental and clinical lights on the rotation therapy, its basis and possibilities. Acta radiol. 23 (1942), 51.
18. — Jensen, H. and Thayssen, V.: Evaluation of different factors in Rotation Therapy. Acta radiol. 25 (1944), 95.
19. — Clinical results with rotation therapy; preliminary report based on 174 cases. Acta radiol. 26 (1945), 361.
20. Strandqvist, M.: Studien über die kumulative Wirkung der Röntgenstrahlen bei Fraktionierung. Acta radiol., Suppl. 55 (1944).

FROM KING GUSTAF V JUBILEE CLINIC IN LUND, SWEDEN
(DIRECTOR: BERTIL EBENIUS)

ROENTGEN ROTATION THERAPY IN CANCER OF THE HYPOPHARYNX[1]

by

Inge Gynning

Rotation therapy can be used advantageously when the lesion to be treated is situated more or less in the middle of the body, when it is deep seated, when the part of the body to be irradiated is cylindrical in shape, and the actual depth dose can be determined. This is usually the case in carcinoma of the thoracic portion of the esophagus, particularly when the lesion is situated in the middle third.

Carcinoma of the hypopharynx, however, will not lend itself so well to such treatment, because the lesion is not deep-seated, with the result that the ratio between the skin-dose and the tumor-dose is less favourable. Furthermore, owing to the conical shape of the neck there may be a considerable difference in the tumor-dose in the upper and lower parts respectively in the treatment of a tumor of the hypopharynx growing down into the esophagus. In such cases roentgen treatment presents considerable dose-problems. Many patients referred to us for therapy already have involvement of the lymph nodes, which, owing to their eccentric position, cannot receive adequate irradiation, and this is another factor limiting the use of the method.

At the Jubilee Clinic, Lund, rotation therapy is used almost exclusively for cancer of the esophagus.

Technique

The patient is placed in the erect position and rotated before a horizontal, fixed roentgen tube. Irradiation is carried out under fluoroscopic control, and the depth dose is measured by means of ionization chambers.

[1] Submitted for publication, Dec. 8, 1950.

Use is made of an 0.5 mm Cu + 1 mm Al filter, the voltage applied being 165 kV 15 mA, the distance between focus and rotation centre, 53 cm and the half value layer, 0.85 mm Cu.

As early as 1942 Prof. EDLING (2) commenced to employ rotation therapy in the treatment of carcinoma of the hypopharynx. As theoretical considerations, however, seemed to be against the efficacy of the method, it was soon discontinued, so that up to 1943 only five patients had received such treatment. Recently, however, the method was readopted.

Results

Of the five patients treated, two developed local recurrences within one year, probably on account of insufficient irradiation (depth dose: approximately 4,500 r within 15 and 21 days in each case).

In one patient, a 58-year-old woman, the tumor responded favourably to irradiation but an untoward irradiation reaction of the tissues in the tumor region and secondary bronchopneumonia set in and the patient died $5^1/_2$ months after the conclusion of the roentgen therapy. A roentgen examination (barium swallow) one month before death showed that some of the barium passed into the trachea. Laryngoscopy disclosed marked edema of the larynx. This finding was verified at autopsy. Microscopy revealed no residue of the very mitotic and cornifying cancer originally diagnosed. The patient had received a daily dose of at least 250 r, the total dose delivered to the actual tumor being about 5,200 r in 20 days.

When last reviewed, October 1950, the other two survivals (7 years after treatment) felt well. Slight marks of irradiation reaction were to be seen in the skin and in the hypopharynx. Both patients were women 62 and 52 years of age and both had a pronounced Plummer-Vinson syndrome.

In these two cases the patients had complained of symptoms only eight and two weeks respectively before the condition was diagnosed and rotation therapy instituted. Each had a growth 4 to 5 cm long. The tumors could be seen laryngoscopicaliy. Microscopy revealed a slightly differentiated tumor in one case (fig. 1) and a medullar, cornifying carcinoma in the other (fig. 2).

In the first case treatment was carried out at 24 sittings. A SIEVERT (3) chamber was passed into the region of the tumor on 17 occasions and the ionization readings were found to be fairly uniform. The average intensity of irradiation in the centre of the field was approximately 24 r per minute. The daily dose varied between 165 r and 240 r. The estimated total depth dose during the course of 26 days was 5,200 r. The field was 4 cm $\times$ 7 cm (in the tumor region).

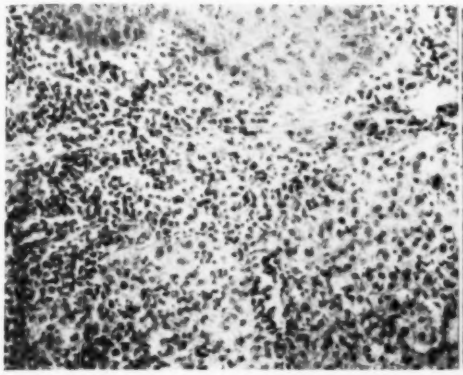


Fig. 1. Lowly differentiated cancer infiltrating under a conserved squamous epithelium (at top of photo).

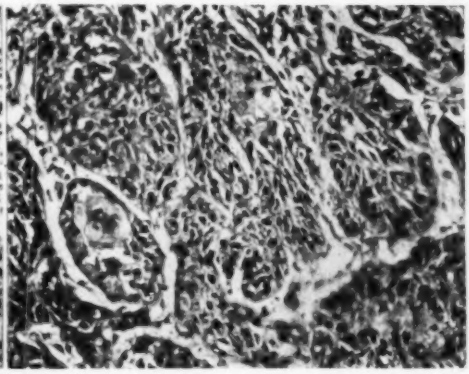
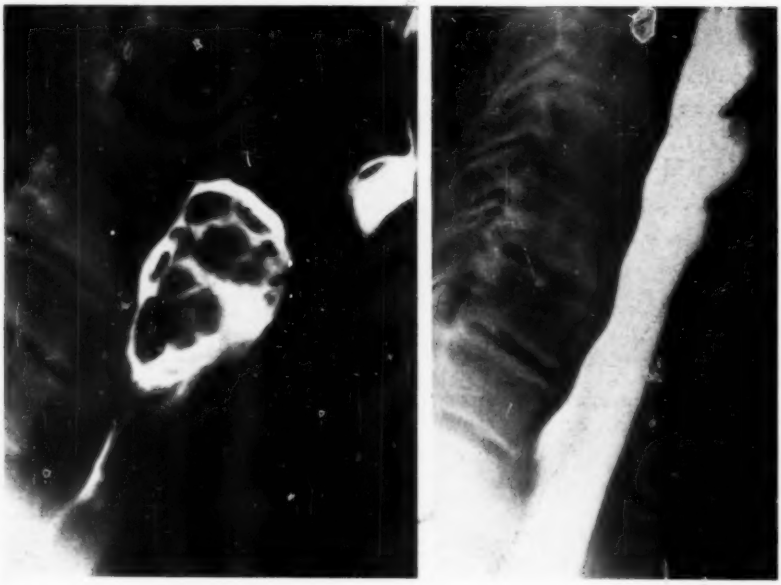


Fig. 2. Infiltrating squamous-cell cancer with tendency to cornify.

In the second case treatment was carried out at 22 sittings. Measurements on 5 occasions showed the intensity of irradiation to be practically uniform. The amount of radiation delivered was the same as in the previous case, *i. e.* 24 r in the centre of the tumor. The daily dose given at the first few sittings was 300 r and later 200 r to 240 r. The total depth dose administered in the course of 24 days was, at the most, 5,200 r. The irradiated field was 5 cm × 10 cm. Irradiation reaction was slightly more marked in this case.

On discharge from hospital no tumor could be seen by laryngoscopy, but there was a reaction of the mucous membrane with considerable edema, hyperemia and the presence of some fibrinous membranes. There was also a local dry epidermitis of the neck.

During the first month after treatment both patients found swallowing difficult and were aphonic. The first patient also developed a small area of local exudative epidermitis on the left side of the neck. After another month the hoarseness disappeared and swallowing no longer caused any trouble. Laryngoscopy revealed moderate edema in the vicinity of the arytenoid region and in the epiglottis but otherwise showed nothing unusual. During the follow-up both patients complained of brief spells of slight hoarseness and dryness of the mouth. These symptoms were, however, mild and in the course of time gradually decreased. When last reviewed (October, 1950) both patients were clinically and roentgenologically free of signs (Fig. 3 and 4) and laryngoscopy showed only very slight mucosal atrophy.

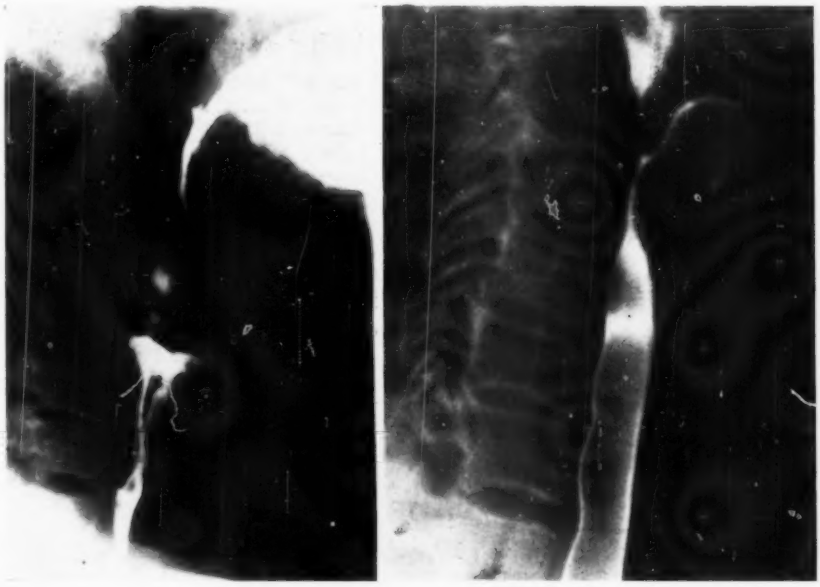


a. b.

Fig. 3. Case 1. a. before treatment, b. after treatment.

In both patients the appearance of the skin is now practically normal except for slight marks of atrophy; there is however still slight submental edema. It may be of interest to mention that before roentgen treatment the second patient had been able to swallow only relatively small boli on account of the Plummer-Vinson syndrome, but is now no longer troubled by dysphagia (Fig. 4). The daily depth dose of 200 r to 240 r in these two cases was heavier than that (200 r) we generally use in the treatment of carcinoma of the esophagus. In both cases there was marked primary irradiation reaction, probably due to the heaviness of the dose. The patient who died from bronchopneumonia had received an even heavier daily dose (250 r), which produced irradiation effects both in the vicinity of the tumor and on the skin. It would therefore seem advisable to employ a smaller daily dose of, say, 200 r. In view of the time factor the total depth dose should then be increased accordingly.

In these cases the depth dose was measured by the introduction of a single chamber. Judging by accumulated experience in the treatment of cancer of the esophagus the depth dosage can be measured more ac-



a. b.

Fig. 4. Case 2. a. before treatment, b. after treatment.

curately if two to four or even more chambers, coupled in series, are introduced at a time. Five measurements are thought to be necessary for estimating the depth dose, although the number necessary in individual cases will depend upon the uniformity of the measurements obtained.

In view of the theoretical considerations mentioned in the introduction and of observations made in the cases described, rotation treatment of carcinoma of the hypopharynx is capable of producing favourable results in cases where the tumor does not extend below the level of the seventh cervical vertebra and where there are no palpable metastases.

SUMMARY

At King Gustaf V Jubilee Clinic in Lund, Sweden, carcinoma of the esophagus is routinely treated with roentgen rotation therapy. During 1942—1943 five microscopically verified cases of cancer in the hypopharynx were also given such treatment. Two of these patients have survived and when last reviewed seven years after treatment, were free of signs. The histories of these two cases are reported and the technique of the method, the dosage and the measurements are discussed.

ZUSAMMENFASSUNG

In der König Gustav V Jubiläumsklinik in Lund, Schweden, werden die Oesophagus-Carcinome gewohnheitsmässig mit der Röntgen-Rotationsbestrahlung behandelt. In den Jahren 1942—43 wurden auch 5 mikroskopisch sichergestellte Hypopharynx-Carcinome mit dieser Methode bestrahlt. Zwei von diesen Patienten leben noch und waren symptomfrei, als sie sieben Jahre nach der Behandlung zum letzten Mal nachuntersucht wurden. Die Krankengeschichte dieser 2 Fälle wird berichtet und die Technik der Methode, die Dosierung sowie die Messungen.

RÉSUMÉ

En Suède à la Clinique du Jubilé de Gustave V à Lund le cancer de l'œsophage est couramment soumis à la thérapie rotative aux rayons roentgen. Durant la période de 1942 à 1943 cinq cas de cancer de l'hypopharynx, vérifiés au microscope, ont été traités ainsi. Deux des malades ont survécu et à la dernière visite, sept années plus tard, ils étaient sans symptômes. Les dossiers de ces deux cas sont exposés. La technique de la méthode, le dosage et les mensurations sont discutés.

REFERENCES

1. Berkman, A. T., Hellmann und Dessauer, F.: Vorläufige Mitteilung über erste Ergebnisse bei der Bestrahlung von Larynx- und Pharynx-Karzinomen mit modifizierten Fraktionsmethoden, insbesondere Rotationsbestrahlung. Radiologia Clinica 8 (1939), 3.
2. Edling, L.: Experience with roentgen rotation therapy. Acta radiol. 25 (1944), 427.
3. Sievert, R.: Über die Anwendung der Kondensatorkammer für sowohl Röntgen- wie γ-Strahlenmessungen; zugleich ein Beitrag zu den Vergleichen der biologischen Wirkungen dieser beiden Strahlenarten. Acta radiol. 15 (1934), 193.

FROM THE DEPARTMENTS OF RADIOLOGY AND PATHOLOGY (PROF. J. H. MULLER), OF THE WOMEN'S HOSPITAL (DIRECTOR: PROF. E. HELD) AND THE MEDICAL POLICLINIC (DIRECTOR: PROF. P. H. ROSSIER), UNIVERSITY OF ZURICH, SWITZERLAND.

A NEW METHOD FOR THE TREATMENT OF CANCER OF THE LUNGS BY MEANS OF ARTIFICIAL RADIOACTIVITY[1]

(Zn^{63} and Au^{198})

First experimental and clinical studies

by

J. H. Muller and *P. H. Rossier*

I. Introduction. Materials and Methods

The »selective» fixation of a short-lived artificial radioactive isotope within the lungs, by means of intravenous application, was realized for the first time in 1946 by the authors (1). The cyclotron-produced radiozinc (Zn^{63}) was injected intravenously in the form of a non-soluble, dispersoid sulfide, suspended in a pectin solution. Experiments on rabbits as well as injections in patients (1 case of metastases of a hypernephroma in the lungs, 1 case of advanced inoperable already irradiated bronchial carcinoma) resulted in an almost complete fixation of the radiozinc within the lungs, obviously by means of a diffuse microembolism of the radioactive particles into the lung capillaries. After the injections of the radiozinc suspension the radioactivity measured within the thoracic area was very intense, whereas practically none was found in blood and urine specimens. Up to 100 millicuries Zn^{63} were administered at a time and the injections were perfectly well tolerated.

In the first case no therapeutic effect was noted, the patient being already in a completely desolate condition. In the second case a notable regression of the bronchus tumor was obtained by application of several

[1] This paper was presented in parts at the International Congress on Radiology of London, July 1950, and at the scientific session of the Swiss League against Cancer, in St. Gall, December 1950; submitted for publication, Febr. 17, 1951.

hundred millicuries of radiozinc in combination with 400 kV-roentgen therapy. The 67 years old patient died 8 months after the treatment of generalized metastases. The autopsy revealed only a small fibrous rest of the originally very large primary tumor, which was a squamous cell carcinoma. This first therapeutic result was an encouragement to aim at further developments of this therapeutic procedure.

Due to the difficult manipulation of the short-lived Zn^{63} (half-life: 38.3 min.) this isotope had no chance to gain clinical value. Only in May 1950 we succeeded in obtaining a substantial experimental and clinical development by using the radiogold (Au^{198}) with a half-life of 65 hours, instead of Zn^{63}. The radiations of the radiogold (0.97 MeV β-rays and 0.44 MeV γ-rays) are also quite suitable.

It is well known that no colloidal radiogold can be administered intravenously in order to obtain a »selective» fixation within the lungs, because the very small gold particles (40—80 $\mu\mu$) pass through the lung capillaries and finally get captured in the reticulo-endothelial system, especially of the liver and spleen. Our own animal experiments showed that by addition of a macromolecular substrate such as pectin no better fixation of the gold colloid within the lungs can be obtained (fig. 1). Contrary to our former opinion the addition of pectin showed to be irrelevant and rather the size of the particles proved to be the decisive factor.

As the particles of the radiozinc used in the first experiments were very much larger than the ones of the colloidal radiogold, we endeavoured to make a gold precipitate of larger particles, also suspended in a pectin solution. With this method we succeeded again in obtaining a »selective» fixation of the artificial radioactivity within the lungs. Fig. 1 and 2 demonstrate this in animal experiments as well as clinically. Before we proceed with the history of the first treated cases we want to give some technical details concerning the radiogold-precipitate.

We made the first adequate Au^{198}-precipitate out of colloidal radiogold. The earlier shipments of radioactive gold colloid were sent by air, through the courtesy of the U. S. Atomic Energy Commission, from the Abbott Laboratories, North Chicago. Since spring 1950 the colloidal radiogold is kindly supplied from the Atomic Energy Research Establishment of Harwell, England, which means substantial savings in shipping costs and losses of activity owing to the shorter distance of air transport. In recent times we made the gold-precipitate out of pure inactive gold in cooperation with Dr. P. JORDAN, radiochemist of the Cyclotron laboratory, Physics Department (director: Prof. Dr. P. SCHERRER) of the Swiss Federal Institute of Technology in Zurich. This precipitate is sent in special irradiation cans to Harwell, where it is made radioactive in the atomic pile and immediately sent back to Zurich by air. In this way the

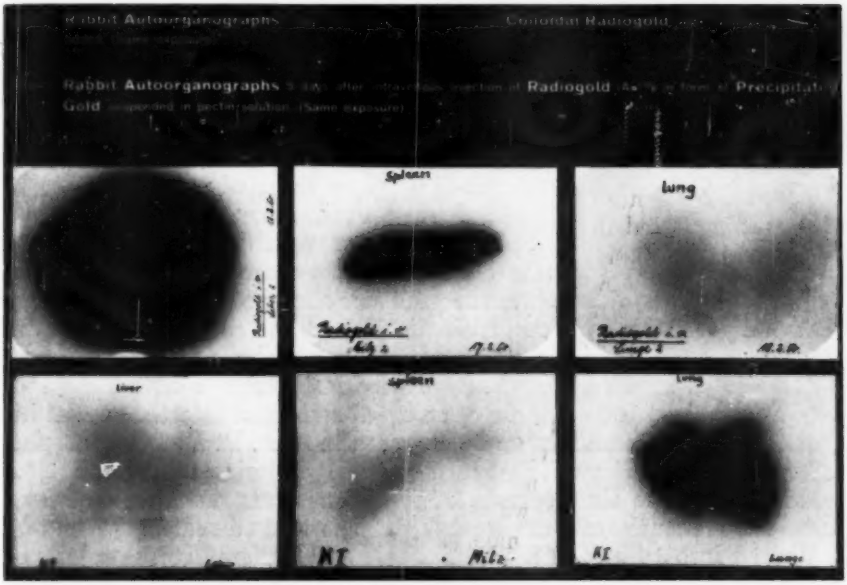


Fig. 1. Above: rabbit auto-organographs 1 day after the intravenous injection of colloidal radiogold (Au^{198}) with pectin solution added. Same exposure. The liver and the spleen are strongly radioactive. The lungs are only slightly radioactive.

Below: rabbit auto-organographs 5 days after the intravenous injection of Au^{198} in form of a precipitate suspended in pectin solution. Same exposure. The liver and spleen are but slightly radioactive. The lungs are strongly radioactive.

Fig. 2. Enlarged autoradiograph of a thin slice of rabbit lung tissue, imbedded in paraffin, 2 days after the intravenous injection of an Au^{198}-precipitate, suspended in pectin solution. Quite even distribution of the radioactive particles within the lung tissue, due to a diffuse microembolism of the Au^{198} into the lung capillaries.

costs can be lowered and the chemical processing of radioactive material avoided. This gold-precipitate is prepared as follows:

The adequate size of the gold particles was determined to be 30—50 μ in diameter, that is about a thousand times larger than the ones of the colloidal gold. Considering the toxicity of soluble gold the particles must be made of non soluble metallic gold. The high specific weight of gold particles of this size and their tendency to conglomerate makes it imperative to use a suitable carrier, which predetermines the particle size.

The carrier substance too must be non toxic and non soluble. Charcoal in form of a highly purified powder was found suitable. The particles averaging 30—50 μ in diameter were selected by means of repeated sedimentation in distilled water under microscopical control. This procedure was performed without any special apparatus and hence the finally obtained charcoal powder still contained a number of larger and smaller particles. The inactive gold is then absorbed by these charcoal particles in form of gold chloride and the gold salt thereafter reduced into metallic gold under the action of oxalic acid in oversaturated hydrochloric solution, without heating but with continuous agitation of the charcoal powder by means of a mechanical device. Once the gold salt absorbed by the charcoal has been fully reduced, the suspension is filtered and carefully washed until the last traces of the chloride and oxalic acid are removed. This gold precipitate is then dried by heat, divided into portions containing about 100 mg gold and 100—120 mg of charcoal and filled into the special irradiation cans of aluminium supplied from the A. E. R. E. This material is later sterilized in Harwell by heating at 100° C during 2 hours and afterwards exposed to the neutrons of the atomic pile, until an activity of 400—500 millicuries of Au^{198} is reached. The returned radioactive material is poured into 15 ccm of a 4 % isotonic and buffered sterile solution of highly purified pectin. A homogeneous suspension is obtained by submitting this mixture to a shaker operating at the frequency of the ordinary alternative current. The techniques used for the injections of this suspension will be described in the following section.

II. First Clinical Intrapulmonary Applications of Radiogold

Intrapulmonary applications of the radiogold precipitate were performed in a first group of 4 patients. These treatments were rather »experimental», but they undoubtedly exhibit many interesting aspects and open new possibilities which might gain definite practical importance within a near future. A short description of these cases will be presented, giving special consideration to the observations and measurements of radioactivity.

Case 1: The first patient[1] who received the intrapulmonal application of the radiogold precipitate is a still living 42 years old man, affected with a severe generalized Hodgkin's disease extensively involving the lungs. At first there was a considerable exudate production in the right pleural cavity which made frequent aspirations necessary. Two intravenous injections of the gold precipitate were given on the 15. 5. and

[1] This first patient was treated at the Medical Division (Chief: P. D. Dr. N. MARKOFF) and at the Radiological Department (consulting chief: Prof. J. H. MULLER) of the Cantonal Hospital of Coire. All the other Au^{198}-patients were admitted on the Ward department of the Medical Policlinic, University of Zurich.

Fig. 3. Thoracic autoradiograph, with supplementary weak roentgen exposure, of a male aged 42 (Au^{198}-case nr. 1) affected with Hodgkin's disease involving the lungs. The picture was obtained after an intravenous injection of Au^{198}-precipitate suspended in pectin solution, with added citrated blood. The radioactivity is exclusively localized within the lungs. The right lung is partly deviated and compressed by a pleural exudate.

1. 6. 50, the total amount deposited in the lungs being about 50 millicuries of Au^{198}. The »selective» fixation of the injected radiogold within the lungs is clearly demonstrated by the thoracic autoradiograph (fig. 3). In spite of a poor general condition and severe dyspnoea the injections were extremely well tolerated and the exudate production in the right pleural cavity stopped immediately.

Technique of the injections: These first precipitates of radiogold had been made out of colloidal radiogold without addition of charcoal powder and were injected in a cubital vein by means of an ordinary syringe. The injected suspension containing the radiogold was made of a 4 % pectin-solution mixed with citrated blood of the patient. A considerable amount of the gold sedimented in the syringe.

In spite of the rather low dosage of the radiogold injected in this case a very substantial improvement of the patients condition was obtained, the most striking result being the »drying out» of the pleural exudate and a definite reduction of the dyspnoea. The patient was then well enough to be submitted to an extensive roentgen therapy including the remnants of the lung infiltrations and a great number of other localizations of the disease. This patient is still relatively well and resumed his work as a hotel porter.

The other three patients on whom this therapeutic procedure was investigated were all cases of inoperable, quite hopeless bronchial carcinoma. For these three cases the intrapulmonal radiogold application was improved by using the catheterisation of the heart. It was the first time, that this technique was utilized for therapeutical purposes. Through intravenous catheterisation of the heart it became possible to localize the radiogold-precipitate within one lung and even within a single lung

Fig. 4. Thoracic autoradiograph, with supplementary weak roentgen exposure, of a male aged 70 (Au^{198}-case nr. 2), affected with extensive squamous cell carcinoma of the bronchus of the right inferior lobe. By means of a catheterisation of the heart the Au^{198}-precipitate, suspended in pectin solution with added heparinized blood, was injected into the arterial branch supplying the right inferior lobe. Observe the strong radioactivity exclusively localized within the corresponding lobe.

lobe, by directing the catheter through which the radioactive material was injected into a predetermined lung artery or into a division branch of it. The »topographic selectivity» of the radiogold applications within the lung tissue became thus more accurate.

Case 2: Male patient, aged 70, unskilled factory worker, admitted on July 5th, 1950. Previous bronchoscopy and biopsy as well as roentgenological findings had demonstrated the presence of a large squamous cell cancer of the main bronchus of the right inferior lobe, causing partial obstruction. The condition was inoperable in consideration of the age of the patient and of the tumor extension.

On the day after admission a heart catheter was introduced through the left cubital vein, pushed into the right ventricle and from there into the inferior branch of the right lung artery, under continual roentgen control. 30 millicuries of gold precipitate prepared as for case nr. 1, suspended in a 4 % pectin solution were injected through the catheter with an ordinary syringe. The thoracic autoradiograph of the following day demonstrated exceedingly well that the radiogold which had been injected through the heart catheter became localized within the inferior lobe of the right lung (fig. 4). Specimens of venous blood collected after the injection were not radioactive at all. — Direct measurements of the radioactivity of the patient's right lung performed at a distance with a directional counter (compared in identical conditions with a known radiogold aliquot) showed that only 15 % of the utilized radiogold had reached the lung, the greater part of the Au^{198}-precipitate having been lost through sedimentation in the syringe and on the catheter walls. This enormous loss of active material made it mandatory to improve the injection technique.

This was done on September 6th, 1950, when after the heart catheter had been localized in exactly the same way in the inferior branch of the right lung artery, the suspension of the radiogold-precipitate was injected

by means of an infusion device, through which an infusion of the patients own heparinized blood was made immediately afterwards under mild pressure, in order to wash out the remnants of sedimentated gold. This improved technique gave a much better yield and only 25 % of the used 140 millicuries of Au^{198} were lost this time in the injection system, 105 millicuries having reached the right lung. The autoradiographic chest control, however, demonstrated a quite even distribution of the radioactivity within the whole right lung, the tip of the heart catheter having apparently been withdrawn into the main pulmonary artery at the moment of the injection. The gold precipitate used at that time was also of a somewhat better quality. The specimens of venous blood taken after the application of this strong preparation of Au^{198} showed no activity so that very little spilling of radioactive material outside the right lung occurred. This second application was again well tolerated by the patient and repeated checks of the morphological blood counts did not demonstrate significant modifications due to the action of radiation.

3 days after the intrapulmonary application of these 105 millicuries of Au^{198} a direct measurement of the γ-radiation emitted at the surface of the chest was performed by means of the thimble chamber of the Integron-Dosimeter, which is calibrated for the radiation of the 400 KV Maximar-Unit — in service in our department for several years.

The emitted γ-radiation was measured during $^1/_{20}$ of a half-life period, the thimble chamber being placed on the skin in the right-anterior axillary line, 4 cm below the nipple. The thus measured roentgens were then integrated over the whole time of activity of the Au^{198} from the time of the injection. This measured integration value of the total amount of γ-radiation emitted was found to be 1 090 *r*. Considering the geometrical factors involved, it is quite clear that the amount of γ-radiation emitted within the lung tissue was still greater. The calculated dose delivered in the right lung over the whole period of activity of the injected radiogold was found to approximate 16,000 roentgen equivalent physical, of which about $^9/_{10}$ correspond to the β-radiation and $^1/_{10}$, *i. e.* 1.600 *rep* to the γ-radiation. This γ-ray dose calculated with the formula $D_B = 76\ C$ (C representing the amount of millicuries per kilogram of tissue), as indicated by Marinelli, Quimby and Hine (2), is in good agreement with the measured dose of 1.090 *r*.

No visible skin reactions were observed on the right chest side of the patient. Such reactions were hardly to be expected, considering the time factor involved, the continuous irradiation being of a very protracted saturation type.

After this second application of Au^{198} the course of the disease remained stationary for a few weeks, then rapidly grew worse and the patient died in a highly cachectic state, October 19th, 1950. The post mortem exami-

nation demonstrated a large carcinoma of the main bronchus of the right inferior lobe, about the size of a man's fist. This squamous cell carcinoma showed histologically a great amount of partly pyknotic, partly gigantic nuclei proving a strong radiation effect upon the tumor cells. Xanthomatous foci were found in the right lower lobe and irregularly shaped gold particles within the capillaries and small arteries of the right lung, but none in the left lung. Some gold particles were also found in the interstitial tissue. The autopsy revealed further large metastases in several ribs and parapancreatic lymphnodes, as well as a dilatation of the heart etc.

Case 3: The third patient who received the intrapulmonal radiogold was a 57 years old salesman admitted in the first days of September 1950, suffering from an extended carcinoma in the peripheral part of the main bronchus of the right upper lobe. On admission there was already definite neurological evidence of brain metastases. In spite of this hopeless condition an experimental intrapulmonary Au^{198} application was decided. As expected this patient died soon after of generalized carcinosis. This gave us the opportunity to perform precise investigations concerning the distribution of radioactive material in the organism.

On September 5, 1950, 135 millicuries of radiogold precipitate were given into the right main pulmonar artery by means of the improved technique of transvenous catheterization of the heart. As a matter of fact the investigated autopsy material revealed later that the whole gold had been »shot» into the right inferior lobe. Obviously the end of the heart catheter had glided at the last moment into the inferior branch of the right pulmonary artery. Accurate measurements of the amount of Au^{198} effectively deposited in the lung were not possible on account of the delirious state of the patient due to the brain metastases — approximately it was 100 millicuries. The chest autoradiograph demonstrated a radioactive focus in the right lung, but no exact topographic projection was possible because the agitated patient scraped of the film material. 11 days after the intrapulmonal radiogold application the patient died. The autopsy revealed an extended squamous cell carcinoma of the right superior bronchus, with innumerable metastases in the parabronchial, hilar, abdominal and inguinal lymph nodes, as well as in both suprarenal glands, in ribs and in both cerebral hemispheres. Large gold particles were found microscopically in the inferior lobe of the right lung, some small ones also in the liver and spleen. There was a miliar silico-anthracosis and oedema of the lungs, also a dilatation of the heart. Since the patient's post mortem examination was performed 13 days after the Au^{198} injection, *i. e.* after less than five half-life periods, there remained still enough radioactivity to be determined in tissue specimens. Pieces of 2 grams each were taken from all the investigated organs and tissues and burnt to ashes. The incinerated material was put into small, shallow quartz dishes of a standard size and

Table 1.

Au^{198} — Case Nr. 3. *Results of the GM-counter measurements.*

Examined organs and tissues	Weights in g (Total weight of body 45 kg)	Activities measured with GM-counter (lots of 2 g of ashed tissue)	Relative activity per g (r. inf. lobe = 100 %)	Extrapolated total activity of the right inferior lobe and of the examined organs and tissues	Activity of the organs and tissues in comparison with right inf. lobe (r. inf. lobe = 100 %)
Right inferior lobe	approx. 250	1,100	100 %	275,000	100 %
Right median lobe (lung tissue)	approx. 150	no measurable activity	—	—	—
Right median lobe (tumor tissue)		0.6	0.055 %	90	0.0033 %
Right superior lobe	approx. 250	1.6	0.145 %	400	0.0145 %
Left superior lobe	approx. 250	1.6	0.145 %	400	0.0145 %
Left inferior lobe	approx. 250	3.5	0.32 %	875	0.032 %
Intrapulmonal lymph node. a.	approx. 10	no measurable activity	—	—	—
Intrapulmonal lymph node. b.	approx. 10	no measurable activity	—	—	—
Spleen	110	144	13.1 %	15,850	5.8 %
Liver	1,520	90	8.2 %	13,680	5 %
Myocard	260	0.4	0.036 %	104	0.0038 %
Kidneys	280	no measurable activity	—	—	—
Skeletal muscle	ap. 20,000	0.4	0.036 %	ap. 8,000	ap. 2.9 %
Testes	36	0.9	0.082 %	32	0.0012 %
Thyroid	25	no measurable activity	—	—	—
Brain	1,800	»	—	—	—
Lumbal vertebra (large piece)	approx. 50	»	—	—	—
Rib (large piece)	approx. 30	»	—	—	—

measured in standard geometrical conditions with an end-window β-ray Geiger-Müller counter, well protected with lead on all other sides. We measured both β- and γ-radiations, since the residual radioactivity was too weak to rely on the γ-radiation only.

The results obtained are compiled in table 1. The figures demonstrate clearly that the Au^{198}-precipitate injected through the heart catheter had been »shot» into the right inferior lobe, as already mentioned. The topographic localization obtained by this procedure within the lungs is really of an astonishing precision. But this high precision resulted in a rather paradoxical state of affairs for this particular patient, since a displacement of the catheter tip at the moment of the radioactive infusion made us entirely miss the target *i. e.* the tumor area in the right superior

Fig. 5 a. Microphotograph of the lung tissue (Au^{198}-patient nr. 3). Numerous (black) gold particles are clearly visible. They are located in the lung capillaries, partly also in the interstitial tissue.

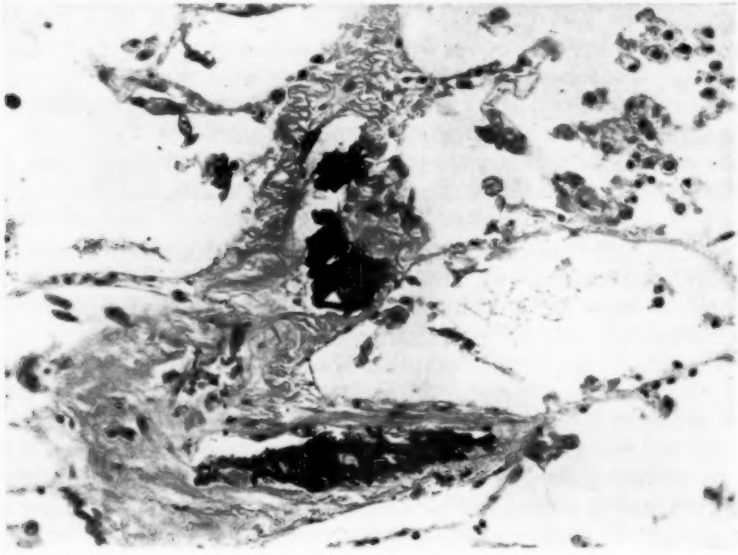


Fig. 5 b. Same lung tissue. Microphotograph at a higher magnification, showing larger gold particles in small arteries.

Fig. 6. Enlarged autoradiograph of a thin slice of the same human lung tissue as in fig. 5, imbedded in paraffin. Observe the rather even distribution of the radioactive foci within the lung tissue. To be compared also with fig. 2.

lobe. Correspondingly no appreciable radiation effect on the tumor cells was found histologically. Nevertheless this observation is of true experimental interest, as it shows that both from the technical and tactical point of view it is advisable to avoid the selection of a too small field of therapeutical action. This is by comparison also the case for the surgical treatment of bronchial cancer, a pneumonectomy being as a rule preferable to a lobectomy.

The particles of the gold precipitate can be clearly seen in the histological sections of the right inferior lobe (fig. 5) and the autohistoradiographs (fig. 6) show the same distribution pattern of the radioactive particles as in previous animal experiments (fig. 2). Measurements of the size of the particles found in the lung tissue were also made possible and gave values ranging from 25 to 60 μ. A few larger particles were found in small arteries (fig. 5 b). The gold precipitate injected to this patient was still not homogeneous, having been prepared from radioactive gold colloid without selected charcoal carrier. Therefore the micro-measurements were of decisive importance and gave the directives for selecting the standard average particle size of 30—50 μ as the most suitable. The production of better gold precipitates by means of charcoal particles of this size became then possible as was described in part I.

The Au^{198}-precipitate of this case having been made without carrier contained also an amount of much smaller particles which glided readily through the lung capillaries and were collected mainly by the RES of the liver and spleen. The amount of radioactive material in these organs, however, did not exceed 5—6 % of the injected Au^{198} and but extremely small radioactive deposits were found in all the other tissues. It is clear that this »spilling» of radioactive material outside the lungs would have been still less if at that time the precipitate with preselected particles could have been already used. The larger particles cannot pass through the filter of the lung capillaries except when a collateral vascularisation has developed within the lungs after long lasting atelectasis etc.

But even the escape of a few millicuries of Au^{198} into the liver and spleen, as it happened in this case, presents no danger. A small number of other patients, who needed a selective irradiation of the liver and

Fig. 7.

Fig. 8.

Fig. 7. Thoracic autoradiograph, with supplementary weak roentgen exposure, of a male aged 55 (Au^{198}-case nr. 4), affected with extensive bronchial squamous cell carcinoma of the right lung, after intrapulmonal application of 150 millicuries of Au^{198}-precipitate. The dosage is 3 times higher in the right lung than in the left one. Pleural exudate on the right side, which deviates and compresses partly the corresponding lung. The Au^{198}-precipitate was injected by means of a catheterisation of the heart.

Fig. 8. Thoracic autoradiograph, with supplementary roentgen exposure, of the same patient as in fig. 7, after intrapleural injection of colloidal Au^{198} (100 millicuries), mixing with exudate in the right pleural cavity. Strong radiation emitted therefrom.

spleen had perfectly well tolerated intravenous injections of colloidal radiogold amounting to 30—50 millicuries (unpublished data).

Case 4: The fourth patient who received an intrapulmonary application of radiogold precipitate by means of catheterisation of the heart was a 55 years old man, suffering from a squamous cell carcinoma of the bronchus of the right median lobe. The diagnosis had been ascertained by bronchoscopy, cyto-histology and tomography, the latter having demonstrated infiltrations of the tumor also around the main bronchus causing considerable stenosis. Electrocardiographic examination had revealed a Tavara-rhythm which made an invasive penetration of the cancer into the pericard and heart auricles probable. There was also a large exudate in the right pleural cavity. The patient was thus considered inoperable.

On November 21, 1950, 150 millicuries Au^{198}-precipitate prepared with the selected charcoal carrier were deposited in the lungs by means of a heart catheter. Half of the infusion was directed into the right ventricle, the other half into the main right pulmonary artery. In this way the right lung received 3 times more radiogold than the left one. The chest autoradiograph (fig. 7) demonstrates the expected distribution of radiation. Owing to the large pleural exudate on the right side the stronger

radiating right lung was kept at some distance from the thoracic wall. From the experience gained in case no. 3, the total pulmonary irradiation with triple dosage on the diseased side was thought to open better initial therapeutic prospects than a localized Au^{198}-application in the right median lobe only.

14 and 22 days later we further injected twice 100 millicuries of colloidal radiogold into the right pleural cavity (fig. 8). This total amount of 200 millicuries of colloidal Au^{198}, evenly mixed with the exudate fluid, did insure a strong irradiation effect upon the diseased pleura and also a convenient cross firing irradiation of the right lung, which hung partly collapsed in the radioactive pleural bath. It was to be expected that a certain amount of the colloidal Au^{198} might be resorbed and collected within the regional lymph nodes, since experimental work has evidenced such a migration of the gold colloid, highly desirable indeed from the therapeutical point of view. We refer for particulars to the paper of SHERMAN, NOLAN and ALLEN (3).

From the Au^{198}-precipitate about 18,000 *rep* were administered to the right lung and 6,000 *rep* to the left lung, of which 10 % would correspond to the effect of the γ-radiation and 90 % to the β-radiation. These dosage factors were calculated as previously mentioned. No satisfactory calculation of the radiation supplied by the intrapleural colloidal gold was possible. However, with the Integron thimble chamber, the γ-radiation emitted at the right thoracic surface was measured during a standard period to time and then integrated over the whole period of the clinical application of the gold colloid, from the time of the injections until the death of the patient, which occurred on December 16, 1950, when a significant residual activity of the intrapleural gold was still available. The figure for this integrated γ-radiation amounts to 1,800 *r*. — In consideration of the fact that the intensity of the γ-radiation directed towards the partly collapsed right lung was at least 30 % higher than measured at the outer thoracic wall, the total γ-irradiation of the right lung can be estimated at 4,000—4,500 *r*.

The large size of the Au^{198}-precipitate particles involving some self-absorption of the electrons in the metallic gold, the calculated figure of about 16,000 *rep* for the β-radiation emitted within the right lung is probably too high. The effect of this β-radiation, however, represents a considerable additional factor.

The radio-therapeutical effect of this intensive combined pleuropulmonal irradiation of a continuous saturation type did not have time to become fully manifested. At first it caused a real improvement in the patient's condition, dissipating the total atelectasis of the right lung, through reduction of the invasive tumor masses obliterating the main bronchus. But then a severe cardiac failure developed, which proved fatal.

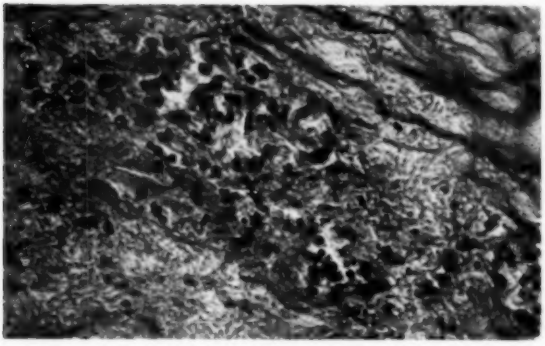


Fig. 9. Microphotograph of tumor tissue near the right main bronchus (same case as in fig. 7 and 8), showing area with advanced necrosis, resulting from the effects of radiation.

The autopsy demonstrated the presence of an extremely large squamous cell carcinoma of the bronchus of the right median lobe, with an extensive invasion of the superior lobe, the pericard and both auricles. This carcinomatous infiltration of the heart muscle had been the immediate cause of death. There were also a few small older infarcts in the right lung, a large parietal thrombus of the right auricle, oedema of the brain, lungs and liver etc.

The microscopical findings concerning the distribution of the radiogold and the effects of radiation are as follows:

A few larger gold particles 15—25 μ in size were found in the histological sections of the spleen. These particles undoubtedly originated from the Au^{198}-precipitate injected into the lungs and had been able to escape through the filter of the lung capillaries. This fact strengthens our previous statements, that the Au^{198}-precipitate particles must have a diameter of at least 30 μ. The pulmonal leakage in this particular case was perhaps slightly facilitated by the moderate collapse and the atelectasis of the right lung, as outlined above. A great number of larger particles were found in the capillaries and small arteries of both lungs, some also in the interstitial tissue, as described in case no. 3. A considerable amount of colloidal gold particles was deposited in the right pleura, especially in parts with pathological thickenings. These findings will be discussed later together with the autohistoradiographs of the pleura.

The tumor tissue exhibited the typical structure of a differentiated squamous cell carcinoma with parakeratosis and extreme invasive growth. An intense irradiation effect was found, partly in form of cytological modifications such as pycnotic or gigantic nuclei, partly in form of necrosis of the tumor tissue, especially within the carcinomatous infiltrations of the heart and around the main bronchus (fig. 9). Outside the tumor area the lung tissue showed moderate oedema and a partly increased amount

Table 2.

Au^{198} — Case Nr. 4. *Results of the GM-counter measurements.*

Examined organs and tissues	Weights in g (Total weight of body 68 kg)	Activities measured with GM-counter (lots of 2 g of ashed tissue)	Relative activity per g (r. pleural exudate = 100 %)	Extrapolated total activity of the examined organs	Activity of the organs and tissues in comparison with right pleural exudate (r. pleural ex. = 100 %)
Exudate from r. pleura	approx. 1,500	1,090	100 %	1,670,000	100 %
Thickened part of right mediastinal pleura with tumor node	specimen weighing a few g	518	47.5 %	—	—
Tissue of right lung with thickened pleura	»	512	47 %	—	—
Right visceral pleura	»	295	27 %	—	—
Right mediastinal pleura	»	286	26 %	—	—
Right lung with visceral pleura (specimen valid for mean activity of the right lung)	approx. 500	190	17.4 %	95,000	5.7 %
Tumor tissue with main bronchus	a few g	7	0.64 %	—	—
Left lung	approx. 500	8	0.73 %	4,000	0.24 %
Spleen	110	12.2	1.11 %	1,340	0.08 %
Liver	1,800	6.6	0.61 %	11,900	0.71 %
Heart (part with tumor infiltration)	400	2.7	0.25 %	1,080	0.065 %
Kidneys	350	1.2	0.11 %	420	0.025 %

of desquamated alveolar cells. It is likely that this finding is partly due to the effects of irradiation.

The autopsy had been performed 26 days after the intrapulmonal application of the Au^{198}-precipitate *i. e.* after the activity decayed over 10 half-life periods, leaving but an extremely weak residual radioactivity. On the other hand there was still present a considerable activity of the colloidal radiogold injected into the right pleural cavity, which gave us a good opportunity to study the distribution of radioactivity in the organism after this modus of gold colloid application. In the same way as in case Nr. 3 pieces of 2 g of the different organs and tissues were incinerated to be measured. Sufficient activity being present, the measurements were performed with a γ-ray counter. The results obtained are compiled in table 2. The figures clearly demonstrate that more than 90 percent of the injected colloidal gold remained, mixed with the exudate, within the pleural cavity. This radioactive exudate, surrounding the partly collapsed right lung, produced mainly a concentric γ-irradiation of

1. Part with normal pleura. 2. Part with thickened pleura. 3. Part with tumor infiltration in thickened mediastinal pleura.

Fig. 10. Slightly enlarged autoradiographs of thin slices of lung tissue with pleura, imbedded in paraffin (same case as in fig. 7, 8 and 9). Observe the strong pleural radioactivity. Very weak residual activity of the lung tissue.

this lung at a short distance, the dosage factors being as already estimated above. The effective distribution of radiation within the lung is rather difficult to ascertain without special investigations on a suitable phantom. Quite remarkable is also the fact that a relatively high superficial uptake of the radioactive gold colloid was found within the pleura, amounting to nearly 50 percent of the average exudate-activity. Moreover, this deposit was particularly high in pleural parts of pathological thickness or with carcinomatous infiltrations. Microscopic examination at high magnification demonstrates clearly that a great amount of small gold particles can be found in these parts up to a depth of a few millimeters, whereas this infiltration due to the transport by histiocytes reaches but little beneath the pleural mesothelium in normal parts of the pleura. These findings, also evidenced by autohistoradiographs (fig. 10), explain the favourable clinical effect of the intrapleural application of colloidal radiogold in cases of pleural carcinosis as already described in our previous papers (4, 8).

Counter measurements and autohistographs demonstrate further, that a weak residual activity due to the gold precipitate injected more than 3 weeks earlier is still present, the mean activity of the right lung being naturally increased by the pleural deposits of the colloidal radiogold. The activities found in all other examined organs and tissues are minimal (less than 1 percent of the mean exudate activity), a fact which proves that but a very small part of the intrapleurally injected 200 millicuries of radiogold was »spilled» into the blood circulation.

A point of special interest is also the previously mentioned possibility of a migration of the colloidal gold particles towards the regional lymph-nodes. The autopsy material was therefore investigated in this respect. All the intrapulmonal and hilar bronchial lymph nodes were moderately enlarged and highly anthracotic. The histological examination of a great number of these lymph nodes of the right lung showed enormous

coal deposits, but only very few true metastatic tumor areas. Quite a number of these lymph nodes were completely imbedded in the infiltrating carcinoma, the highly anthracotic nodes being free from tumor tissue or but slightly infiltrated at the surface only. The lymph vessels and glands were obviously completely stuffed with coal particles, this chronic anthracosis being a major hindrance for the metastatic involvement of the glands, and, as was also to be expected, for a migration of the colloidal gold particles from the pleura into the lymphatic system of the right lung. In fact, no increased radioactivity was found in these lymph nodes as a great number of them were carefully extracted from the surrounding tissues and measured with the γ-ray counter.

In spite of a negative finding in this particular case, such a lymphatic uptake of the colloidal radiogold after its intrapleural injection might be possible under suitable conditions. This hypothesis is strongly supported by the already mentioned experimental investigations of SHERMAN, NOLAN and ALLEN (3) and also by an autopsy finding of JENTZER and WENGER (5), who found a substantially increased radiogold concentration in retroperitoneal lymph nodes after an intraperitoneal injection of colloidal Au^{198} administered in a case of abdominal carcinosis, along the therapeutical lines we have previously indicated (4, 6, 7, 8) for cases of extended ovarial carcinoma.

Discussion

The herein described procedure allows the hitherto unrealized »selective» irradiation of the lung tissue by means of a short-lived and chemically innocuous artificial radioactive isotope. The radioactive gold (Au^{198}) is very suitable for that purpose. The qualitative and quantitative aspects of this procedure, in particular its high grade of »topographic selectivity», open the way to a presumably efficient treatment of lung malignancies. No limiting factors are set from the technical side, yet many difficult clinical problems are involved.

The reported first practical achievements bear the features of »experimental» development. They point out that definite clinical improvement was obtained in a case of severe Hodgkin's disease of the lungs in spite of a low radioactivity dosage. On the other hand cases of bronchial carcinoma which were incurable owing to extensive metastases or invasive tumor growth into the heart could not be significantly improved by this new therapeutical approach. Thus further practical developments will have to rest mainly on a skilful choice of the cases for which reasonable chances are available and also on the appropriate tactical planning of the treatment.

The clinical indications of the intravenous applications of the Au^{198}-precipitate would be all diffuse lung malignancies of a sufficient radiosensibility level, such as the already mentioned lymphogranuloma, as well as some types of primary or metastatic carcinoma and sarcoma of the lungs. It is quite probable that latent lung metastases of a number of tumor types in the pre-clinical *i. e.* pre-roentgenological stage of development might be successfully combated by this procedure, since the radioactive particles are projected into the lung capillaries in the way of a diffuse micro-embolism, following exactly the same paths as the embolized tumor particles. It would undoubtedly be of great interest to investigate this procedure among a selected group of cancer patients in which a high probability of a metastatic extension to the lungs is to be expected, since the problem of controlling such extension in the earliest stages is of utmost importance keeping in view the prevention of haematogenic generalization. — As a supplement to the conventional treatments this intrapulmonal application of radioactivity could also yield favourable therapeutical effects upon some diffuse, non malignant chronic inflammatory conditions of the lungs.

Taking into consideration the more or less localized malignancies, it can be reasonably expected that some forms of oat cell lung carcinoma might respond favourably to this therapeutic procedure. The bronchus carcinoma is also a type of tumor which might very possibly gain good therapeutic prospects by this method. This would be a matter of importance, since this rather frequent cancer is quite often detected only at an inoperable stage and since its conventional radiotherapy is, as a rule, of but little benefit. The following logical deductions should then be taken into account: According to our previous experience the intrapulmonal application and topographical localization of the Au^{198}-precipitate by means of catheterisation of the heart is a method which demands utmost precision, as the injected radioactive material becomes exactly localized within the area of lung tissue depending upon the catheterized lung artery or one of its selected subdivision branches. If a too restricted field of therapeutical action is chosen *i. e.* but a lobar one, it might occur that the spray of the radioactive projectiles bypasses the tumor, as happened in Au^{198}-case nr. 3. The appropriate tactical planning of such radiogold treatments must therefore be carefully considered. The best way appears to be the application of a minor part of the radioactive material to both lungs and of its major part into the lung containing the carcinoma, as was done in Au^{198}-case nr. 4. A lobar application would only be appropriate at the end of this concentric attack upon the tumor bearing area.

This intrapulmonal application of the Au^{198}-precipitate can be further supplemented by intrapleural injections of colloidal radiogold which are easy to perform, when a pleural exudate is present, as was demonstrated

in Au^{198}-patient Nr. 4. If necessary an artificial hydro-pneumothorax could be performed for that purpose. Such a procedure would also permit a regulated collapsotherapy of the diseased lung, the results of which cannot be discussed yet. Another supplementary procedure to be envisaged is the direct infiltration of the tumor area with colloidal radiogold on the transthoracical or endobronchial route. Such a supplementary application of radioactivity which, in our experience, yielded encouraging preliminary results in the field of gynecological tumor therapy (9 and 10) presents however some dangerous aspects within the thoracic region. This applies also to the combination with endobronchial applications of radioactive bodies, along the lines of »conventional» radium-therapy, which involves the danger of bronchus necrosis and formation of lung abscess.

Most likely a combination with deep roentgen therapy could be useful at the end of a series of Au^{198}-treatments, when the tumor shrinkage has reduced the volume of tissue to be irradiated as much as possible.

Last but not least there is a possibility of combining the intrapulmonal application of the Au^{198}-precipitate with major surgery. Such operative procedure might become possible in some primarily inoperable cases, where both the size of the tumor and its biological grade of malignancy had been reduced through Au^{198}-treatment of moderate dosage. Finally the surgical removal of a lung or lung part which has lost its functional value after administration of a maximum dosage of the radiogold precipitate might also be considered in selected cases.

Acknowledgements: We wish to thank Prof. SCHERRER and Prof. PREISWERK for supplying the radiozinc and for valuable physical discussions, Dr. JACOBI and Dr. JORDAN for their radio-chemical contributions, Prof. VON MEYENBURG and Prof. ZOLLINGER of the University Institute of Pathology for providing autopsy specimens and some of the microphotographs, P. D. Dr. MAIER for performing the heart catheterizations and Miss ELIZABETH PLETSCHER for her technical assistance.

SUMMARY

The clinical development of selective fixation of artificial radioactivity within the lungs is shown. Au^{198} in the form of a precipitate, with particle size 30—50 μ in a pectin-containing solution with the addition of heparinized blood of the patient is used instead of Zn^{63}, which has a much shorter half-life period than Au^{198}. By intravenous injection diffuse microemboli in the lung tissue are obtained. Through a heart catheter inserted into a selected pulmonary artery the radioactivity can be localized in the corresponding part of the lung — up to 150 mC have been injected. This new therapeutic procedure was carried out in 2 patients with Zn^{63} and in 4 patients with Au^{198} (1 case of pulmonary metastases of a hypernephroma, 1 case of pulmonary lymphogranuloma and 4 cases of inoperable bronchial carcinoma). The method may be combined with intrapleural or intratumoral injections of colloidal Au^{198} as well as with classical radiotherapy or surgical operations.

ZUSAMMENFASSUNG

Die klinische Entwicklung einer Methode für selektive Fixation künstlicher Radioaktivität in den Lungen wird beschrieben. Präzipitate von Au^{198} mit einer Partikelgrösse von 30—50 μ, in einer 4 % Pektinlösung suspendiert und mit Zusatz von Eigenblut, wurden verwendet anstatt Zn^{63}, das eine viel kürzere Halbwertszeit als Au^{198} hat. Durch intravenöse Injektion wird ein diffuser Mikroembolismus in dem Lungengewebe hervorgerufen. Durch Einführung eines Herzkatheters in eine bestimmte Lungenarterie kann man die Radioaktivität in den entsprechenden Teil der Lunge lokalisieren. Radiogold bis zu 150 mC ist auf diese Weise injiziert worden. Dieses neue therapeutische Verfahren gelangte bisher bei 2 Patienten mit Zn^{63} und bei 4 Fällen mit Au^{198} (1 Fall von Lungenmetastasen eines Hypernephroms, 1 Fall von Lymphogranulom der Lungen und 4 Fälle von inoperablem Bronchuskarzinom) zur Anwendung. Die Methode kann mit intrapleuralen und intratumoralen Injektionen von kolloidalem Radiogold kombiniert werden, ebenso mit der klassischen Röntgentherapie und mit chirurgischen Eingriffen.

RÉSUMÉ

Les développements cliniques d'un procédé pour obtenir une fixation sélective de la radioactivité artificielle au niveau des poumons sont présentés. Au^{198} sous forme d'un précipité, grandeur de particule 30—50 μ, en suspension dans une solution de pectine, avec adjonction de sang héparinisé du malade, a été utilisé au lieu de la préparation Zn^{63} qui a une période de demie-valeur bien plus courte que l'or radioactif. Par injection intraveineuse il est possible d'obtenir une microembolisation diffuse dans le tissu pulmonaire. En introduisant une sonde veineuse dans une des artères pulmonaires on peut obtenir une localisation de la radioactivité dans la partie correspondante du poumon. Jusqu'à 150 mC d'or radioactif ont été ainsi injectés. Cette méthode nouvelle a été appliquée chez 2 malades avec le radiozinc et chez 4 malades avec l'or radioactif (1 cas de métastases pulmonaires d'un hypernéphrome, 1 cas de lymphogranulomatose des poumons et 4 cas de cancer inoperable des bronches). Elle peut être combinée à l'application intrapleurale ou intratumorale directe d'or radioactif colloïdal, ainsi qu'à la radiothérapie et à la chirurgie classiques.

REFERENCES

1. Muller, J. H., & Rossier, P. H.: Experientia III (1947), 75.
2. Marinelli, L., Quimby, E. & Hine, G.: Nucleonics II/4 (1948), 56 and II/5 (1948), 44. Am. J. Roentgenol. 53/2 (1948).
3. Sherman, A. I., Nolan, J. F. & Allen, W. M.: Am. J. Roentgenol. 64 (1950), 75.
4. Müller, J. H.: Gynaecologia 129 (1950), 289.
5. Jentzer, A. & Wenger, P.: Rev. méd. Liège V (1950), 425.
6. Müller, J. H.: Experientia I (1945), 199.
7. —: Bull. schweiz. Akad. d. med. Wissensch. V (1949), 484.
8. —: Strahlenther. 85/1 (1951).
9. —: Experientia II (1946), 372.
10. — & Held, E. R.: Gynaecologia 131/6 (1951), 385.

(after a black-and-white drawing by Irmgard Grashey-Straub)

RUDOLPH GRASHEY

In Memoriam

On September 24th, 1950, after a long period of illness, RUDOLF GRASHEY passed away at the age of nearly seventy-five. In him we have lost one of the most prominent roentgenologists of the first generation of our science.

GRASHEY was the descendent of a family of physicians. He worked as an assistant at various university clinics in Munich, *e. g.* under v. BAUER in Internal Medicine and v. WINKEL in Gynecology. He was assistant, under v. ANGERER and SAUERBRUCH, until 1920, at the surgical clinic of the Munich University Hospital, where he was in charge of the Roentgen laboratory. Following the publication of a thesis in 1907, characteristically enough on the roentgen diagnosis of bone fractures, he became assistant professor of surgery. In the year 1924 this assistant professorship was extended to include medical radiology as well, a branch which

had in the meantime attained a continually increasing independence. He was appointed professor at the University in 1911. During the period 1920 to 1928 he was Chief of the Roentgen Institute of the large Munich-Schwabing City Hospital. When GRASHEY was appointed professor of Medical Radiology in 1928 at the University of Cologne, he was the first to be so appointed in Germany. Simultaneously he was appointed Director of the University Roentgen and Light Institute. He was Dean of the Medical Faculty in 1931/1932. GRASHEY stayed on working in Cologne until his institute was destroyed at the end of 1944. He then moved to the Charité Hospital in Berlin, where he carried on his work indefatigably up to 1949 under very difficult postwar conditions.

GRASHEY has been awarded manifold honours. He was elected President of the German Roentgen Society several times and given corresponding or honorary member ship of many foreign roentgen societies. He was also an honorary member of almost every medical-scientific society in Germany.

Since GRASHEY had commenced his medical career as a surgeon, it is not surprising that he had already begun to work on the roentgenology of bones during the first years of this century. He was faithful to this field of work throughout his life. It may be said that he, together with ALBAN KÖHLER, with whom he was a close friend, is the founder of roentgenological osteology. A large number of scientific works, all of which cannot be mentioned here, bear witness to this fact. Every radiologist, at least in Germany, knows of his »Atlas typischer Röntgenbilder vom normalen Menschen», which appeared as early as 1905 and reached its seventh edition in 1950. It was translated into several foreign languages. To this day it is the basis of bone roentgenology in German medicine. Soon after that he published his »Atlas chirurgisch-pathologischer Röntgenbilder», which reached three editions. GRASHEY also wrote the chapter on »Die Röntgenuntersuchung in der Chirurgie» in one of the earliest textbooks of roentgenology, that of RIEDER and ROSENTHAL. He has further revised the chapters on »Allgemeine Aufnahmetechnik und Deutung der Röntgenbilder» in the textbook by GERHARTZ and »Röntgenuntersuchung der Knochen und Gelenke» in the handbook on biological working methods by ABDERHALDEN. Volume IX, »Röntgenologie», in the SCHJERNING handbook on medical experiences in the First World War was written by GRASHEY. He had a special interest in the variations of bones as manifested in his »Röntgentafel des Skeletts», a work which can be seen in every roentgen institute in Germany. Three editions of the »Röntgentafel» were published, the last one appearing shortly before GRASHEY's death.

GRASHEY found another great field of interest in the localizations of foreign bodies. His first work, »Röntgenskopische Operationen im tag-

hellen Raum», was, in fact, breaking new ground in this field. In it he described his monocular cryptoscope for the first time. These works of GRASHEY's proved to be of great value during the First World War. He was then the director of special hospitals for wounded with retained shell fragments. GRASHEY's last comprehensive study of this kind of work is his book on »Steckschuss und Röntgenstrahlen», 1940, Georg Thieme Verlag.

His work in the publication of the first volume of the ALBERS-SCHÖNBERG »Röntgentechnik» in 1941 should also be mentioned.

In the field of radiotherapy GRASHEY was especially interested in roentgen-ray injuries, and published several shorter papers on these studies.

As the first holder of a professorship of Medical Radiology, GRASHEY had a great influence on the teaching of this new science. Many roentgenologists received their training under him.

Still more important is the fact that from 1921 GRASHEY was editor of the »Fortschritte auf dem Gebiete der Röntgenstrahlen» and its supplements, as well as of the later-appearing accessory journal, »Röntgenpraxis». In his capacity as editor of the first roentgen journal in the world, started by ALBERS-SCHÖNBERG, GRASHEY has exercised the greatest influence on the development of international medical radiology. Until the last days of his life he bestowed his devoted care upon this journal. As its excellent and skilful editor, he became a friend and supporter of many German and foreign radiologists.

GRASHEY was a doctor in the highest sense of the word, who never forgot human beings for the technique of his science. To his pupils and colleagues he was always the understanding teacher and adviser. Thanks to his kind heart and sense of humour, as well as his deep understanding of the fine arts and the beautiful side of life, he was able to master the hard blows of Fate, which he was not spared, as well as to stand the difficult war and postwar years.

Rolf Glauner

7th INTERNATIONAL CONGRESS OF RADIOLOGY, 1953

Preliminary Notice

In accordance with the decision of the International Committee of Radiology which met in London in July, 1950, the 7th International Congress of Radiology will take place in Copenhagen in 1953. The dates of the Congress will be July 19th — 25th.

The officers for the Congress are as follows:

Honorary president:	Prof. NIELS BOHR
President:	Prof. P. FLEMMING MØLLER
Vice-Presidents:	Dr. Sv. A. CHROM (Diagnosis)
	Dr. JENS NIELSEN (Therapy)
	Prof. CARL KREBS (Biology)
	Prof. H. M. HANSEN (Physics)
	Dr. E. DE FINE LICHT (Technical Section & Exhibition)
Treasurer:	Mr. AAGE VON BENZON, Banker
Secretary-General:	Prof. FLEMMING NØRGAARD

Radiologists from throughout the world will be welcome at the Congress. All national radiological societies are being asked to supply a list of their members, and full details about registration for the Congress will be sent to all radiologists individually as soon as they are available.

Correspondence should be addressed to the Congress Office at 10 Øster Voldgade, Copenhagen K, Denmark.

June, 1951.

FLEMMING NØRGAARD
Secretary-General.

Index to Volume XXXV

Roentgen Diagnostics

Nervous System

Pag.

Carotid body tumours 115
Encephalography in cerebral atrophy 277
Calcifications following ventricular puncture 304
Sturge-Weber syndrome 387

Digestive Tract

Strangulating obstructions 85
Experimental ileus 101
Diverticulosis of gallbladder 133
Zwerchfellschussverletzung 165
Cholecystitis emphysematosa 200
Hodgkin's disease of oesophagus 371
Neurosarcoma duodeni 407

Heart and Vessels

Carotid body tumours 115
Percutaneous carotid angiography 137
Arteriography in malignant tumours..... 309
The cardiac volume 413

Lungs, Pleura and Mediastinum

Zwerchfellschussverletzung 165
Pulmonary changes in fibrosis of pancreas 233
Mediastinal tumour 299

Diseases and Fractures of Bones and Joints

Basilar impression 124
Hurler's syndrome 331

Uro-Genital System

Urethral diverticulum 27
Antihistaminic prophylaxis in urography.. 65
Ureterocele 146
Pyelo-ureteritis cystica 363

Radiotherapy

Carcinoma of hypopharynx 1, 443
Artificial radioactivity 49, 257, 449
Pregnancy in Hodgkin's disease 71
Carcinoma of oesophagus 207, 428
Classification of cervical cancer 230
Hodgkin's disease of oesophagus 371
Vertebral hemangioma 400

Hormone Therapy

Stilboestrol in cancer of prostate 76

Radiobiology

Pag.

Changes caused by alpha-particles in skin of mice 149
Distribution du phosphate de chrome radioactif 257
Matter, life and radiation 293
Subcutaneous application of metallic polonium 356

Technique

Roentgen Examination

Relation between tension and exposure times 22
Fine-grained emulsions for microradiography 33
Magnetic guidance of catheter 62
Addition of antihistaminic agents to contrast media..... 65
Tomography in basilar impression 124
Levelling of contrast in radiographic printing 179
Photo-fluorographic technique 221
Bronchography 246
Effect of focal size on representation of small metal objects 265
Equipment for microradiography 345

Radiotherapy

Artificial radioactivity 49, 449
Planning technique for deep-seated tumours 250
A flexible indicator 313
The mesothorium-radium beam unit 375

Protection

Protective power of roentgen gloves 45

General

Classification of cervical cancer 230
The WHO subcommittee on cancer registration 319

Obituaries

Christian Ingerslev Baastrup..... 326
Rudolph Grashey 469

Editorial

Northern Association for Medical Radiology 231
International Congress of Radiology, 1953 472

List of Authors

Běhounek, F., 375
Bichel, Jørgen, 371
Bierman, A., 22
Boldingh, W. Hondius, 22
Brobeck, Olaf, 27

Clemmesen, Johannes, 319

Dahl, Olof, 250
enstad, Torfinn, 309
Devik, Finn, 149, 356
Di Chiro, Giovanni, 299, 387
Dogan, Sergije, 124

Edling, Lars, 326
Elliot, Allan, 407
Engström, Arne, 33, 345

Falk, Bengt, 304
Frantzell, Arne, 265
Frimann-Dahl, J., 85, 101

Gilbert, René, 71
Glauner, Rolf, 469
Glücker, L., 133
Govaerts, Jean, 257
Gvozdanović, Vladimir, 124
Gynning, Inge, 428, 443

Hansson, Carl Johan, 407
Haubrich, R., 165
Herve, André, 257

Idbohrn, Hans, 115

Jacobsson, Folke, 1

Kjellberg, Sven Roland, 413
Klumpar, Josef, 375
Koppang, Knut, 137
Kreyberg, Leiv, 356
Köhler, Rolf, 207

Lindström, B., 33
Lindgren, Erik, 277, 387
Lindqvist, Inge, 400
Lönroth, Henrik, 413

Mattsson, Ove, 179, 313
Muller, J. H., 449

Nelson, Arne, 221
Nordenström, Björn E. W., 246
Norlin, Uno A. T., 246

Olsson, Olle, 65

Petersen, Gísli Fr., 363

Qvist, Carl F., 200

Roelsgaard, Mogens, 76
von Ronnen, J. R., 146
Rosendal, Thomas, 233
Rossier, P. H., 449
Rudhe, Ulf, 413

Smithers, D. W., 49
Steinert, Ragnar, 45

Thomsen, Gregers, 331
Tillander, Hans, 62

Wegstedt, L., 345
van der Werff, J. Th., 293
Vesterdal, Jørgen, 331